

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 204403

Name: Rivastigmine Transdermal System
4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3mg/24 hr

Sponsor: Alvogen Pine Brook LLC

Approval Dates: August 31, 2015 and September 3, 2015

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
ANDA 204403**

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 204403

APPROVAL LETTERS



ANDA 204403

ANDA APPROVAL

Alvogen Pine Brook, Inc.
10 Bloomfield Avenue
Building B
Pine Brook, NJ 07058
Attention: Patricia Jaworski
Vice President, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated June 12, 2012, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), for Rivastigmine Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr.

Reference is made to your correspondence dated August 31, 2015. Reference is also made to our letter dated August 31, 2015, granting final approval to your Rivastigmine Transdermal System 13.3 mg/24 hr, and granting tentative approval to your Rivastigmine Transdermal System, 4.6 mg/24 hr and 9.5 mg/24 hr.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly your ANDA for Rivastigmine Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr, is **approved**, effective on the date of this letter. The Division of Bioequivalence has determined your Rivastigmine Transdermal System, 4.6 mg/24 hr, and 9.5 mg/24 hr, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Exelon Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr, of Novartis Pharmaceuticals (Novartis).

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA. The “interim” dissolution specifications are as follows:

USP Apparatus:	Modified USP Type VI (Rotating Cylinder)
Rotational Speed:	50 rpm
Temperature:	32 ± 0.5°C
Media:	0.9% NaCl
Volume:	500 mL

Specification:	1 hour:	(b) (4)
	2 hours:	
	4 hours:	
	9 hours:	
	24 hours:	

The “interim” dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement – Changes Being Effected when there are no revisions to the “interim” specifications or when the final specifications are tighter than the “interim” specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The RLD upon which you have based your ANDA, Novartis’s Exelon Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr, is subject to periods of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the “Orange Book”), U.S. Patent Nos. 6,316,023 (the '023 patent) and 6,335,031 (the '031 patent) are both scheduled to expire on January 8, 2019.

Your ANDA contains paragraph IV certifications to each of the patents under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that these patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Rivastigmine Transdermal System, 4.6 mg/24 hr and 9.5 mg/24 hr, under this ANDA. You have notified the agency that Alvogen Pine Brook, Inc. (Alvogen) complied with the requirements of section 505(j)(2)(B) of the FD&C Act, and litigation for infringement of the ‘023 and ‘031 patents was brought against Alvogen within the statutory 45-day period in the United States District Court for the District of Delaware [Novartis Pharmaceuticals, et. al. v. Alvogen Pine Brook, Inc., et. al., Civil Action No. 1:13-cv-00052-RGA]. You have notified the Agency that the United States District Court for the District of Delaware determined that your 4.6 mg/24 hr and 9.5 mg/24 hr products do not infringe these patents.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

**William P.
Rickman -S**

For Carol A. Holquist, RPh
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Digitally signed by William P. Rickman -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=1300043242,
cn=William P. Rickman -S
Date: 2015.09.03 16:59:45 -04'00'



ANDA 204403

APPROVAL/TENTATIVE APPROVAL

Alvogen Pine Brook, Inc.
10 Bloomfield Avenue
Building B
Pine Brook, NJ 07058
Attention: Patricia Jaworski
Vice President, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated June 12, 2012, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), for Rivastigmine Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr.

Reference is also made to the tentative approval letter issue by this office on July 22, 2015, and to your amendment dated August 5, 2015.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, your Rivastigmine Transdermal System, 13.3 mg/24 hr, is approved, effective on the date of this letter. However, we are unable to grant final approval to your Rivastigmine Transdermal System, 4.6 mg/24 hr and 9.5 mg/24 hr, at this time because of the exclusivity issue noted below. Therefore, only your Rivastigmine Transdermal System, 13.3 mg/24 hr is **approved**, effective on the date of this letter. The 4.6 mg/24 hr and 9.5 mg/24 hr strengths are **tentatively approved**.

The referenced listed drug (RLD) upon which you have based your ANDA, Exelon Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr, of Novartis Pharmaceuticals (Novartis), is subject to periods of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent Nos. 6,316,023 (the '023 patent) and 6,335,031 (the '031 patent) are both scheduled to expire on January 8, 2019.

Your ANDA contains paragraph IV certifications to each of the patents under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that these patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Rivastigmine Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr, under this ANDA. You have notified the agency that Alvogen Pine Brook, Inc. (Alvogen) complied with the requirements of section 505(j)(2)(B) of the FD&C Act, and litigation for infringement of the '023 and '031 patents was brought against Alvogen within the statutory 45-day period in the United States District Court for the District of Delaware [Novartis Pharmaceuticals, et. al. v. Alvogen Pine Brook, Inc., et.

al., Civil Action Nos. 1:13-cv-00052-RGA (4.6 mg/24 hr and 9.5 mg/24 hr products) and 13-cv-0370 (13.3 mg/24 hr product)]. You have notified the Agency that the United States District Court for the District of Delaware determined that your 4.6 mg/24 hr and 9.5 mg/24 hr products do not infringe these patents. The same Court also entered a Joint Stipulation of Dismissal for the 13.3 mg product. Under section 505(j)(5)(B)(iii) of the FD&C Act, your ANDA is eligible for approval.

With respect to 180-day generic drug exclusivity, we note that Alvogen was the first ANDA applicant to submit a substantially complete ANDA for Rivastigmine Transdermal System, 13.3 mg/24 hr with a paragraph IV certification. Therefore, with this approval, Alvogen is eligible for 180 days of generic drug exclusivity for Rivastigmine Transdermal System, 13.3 mg/24 hr. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the FD&C Act, will begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA informing the agency of the date the exclusivity begins to run.

I. Approval of Rivastigmine Transdermal System 13.3 mg/24 hr

The Division of Bioequivalence has determined your Rivastigmine Transdermal System, 13.3 mg/24 hr to be bioequivalent and, therefore, therapeutically equivalent to the RLD, Novartis' Exelon Transdermal System, 13.3 mg/24 hr.

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA. The "interim" dissolution specifications are as follows:

USP Apparatus:	Modified USP Type VI (Rotating Cylinder)	
Rotational Speed:	50 rpm	
Temperature:	32 ± 0.5°C	
Media:	0.9% NaCl	
Volume:	500 mL	
Specification:	1 hour:	(b) (4)
	2 hours:	
	4 hours:	
	9 hours:	
	24 hours:	

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement – Changes Being Effected when there are no revisions to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

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The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is

identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at

<http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. The SPL will be accessible via publicly available labeling repositories.

II. Tentative Approval of Rivastigmine Transdermal System, 4.6 mg/24 hr and 9.5 mg/24 hr

We are unable to grant final approval to your Rivastigmine Transdermal System, 4.6 mg/24 hr and 9.5 mg/24 hr. Prior to the receipt of your ANDA insofar as this strength, another ANDA applicant submitted an ANDA for Rivastigmine Transdermal System, 4.6 mg/24 hr and 9.5 mg/24 hr, containing a paragraph IV certification. This other ANDA, therefore, is eligible for 180-day generic drug exclusivity under section 505(j)(5)(B)(iv) of the FD&C Act for Rivastigmine Transdermal System, 4.6 mg/24 hr and 9.5 mg/24 hr. Your ANDA insofar as the 4.6 mg/24 hr and 9.5 mg/24 hr strengths will be eligible for final approval upon the expiration of the other applicant’s 180-day exclusivity, or that exclusivity is otherwise resolved.

Our decision to grant tentative approval to your Rivastigmine Transdermal System, 4.6 mg/24 hr and 9.5 mg/24 hr, is based upon information currently available to the agency (i.e., data in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This decision is subject to change on the basis of new information that may come to our attention.

To reactivate your ANDA prior to final approval of the 4.6 mg/24 hr and 9.5 mg/24 hr strengths, please submit a **“MINOR AMENDMENT TO ORIGINAL #2 – FINAL APPROVAL REQUESTED”** 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a **MINOR AMENDMENT TO ORIGINAL #2– FINAL APPROVAL REQUESTED**.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' cGMPs are subject to agency review before

final approval of the ANDA will be made. Such changes should be categorized as representing either “major” or “minor” changes to Original #2, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the FD&C Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the FD&C Act. Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under section 505 of the FD&C Act, and will not be listed in the “Orange Book.”

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

For further information on the status of this ANDA, or prior to submitting additional amendments, please contact Andrew Potter, Regulatory Project Manager, at (240) 402-9266.

Sincerely yours,

William P. Rickman -S

Digitally signed by William P. Rickman -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=1300043242,
cn=William P. Rickman -S
Date: 2015.08.31 15:39:31 -0400'

For Carol A. Holquist, RPh
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research



ANDA 204403

TENTATIVE APPROVAL

Alvogen Pine Brook, Inc.
10 Bloomfield Avenue
Building B
Pine Brook, NJ 07058
Attention: Patricia Jaworski
Vice President, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated June 12, 2012, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), for Rivastigmine Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr.

Reference is made to the Complete Response letter issued by this office on July 25, 2014, and to your amendments dated October 2 and October 10, 2014; January 6, February 18, May 14, June 16, and June 17, 2015.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the exclusivity issue noted below. Therefore, the ANDA is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practice (cGMP) at the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to our attention. This letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the FD&C Act.

The reference listed drug (RLD) upon which you have based your ANDA, Exelon Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr, of Novartis, is subject to periods of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent Nos. 6,316,023 (the '023 patent) and 6,335,031 (the '031 patent) are both scheduled to expire on January 8, 2019.

Your ANDA contains paragraph IV certifications to each of the patents under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that these patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Rivastigmine Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr, under this ANDA. You have notified the agency that Alvogen Pine Brook, Inc. (Alvogen) complied with the requirements of section 505(j)(2)(B) of the FD&C Act, and litigation for infringement of the '023 and '031 patents was brought against

(Alvogen) within the statutory 45-day period in the United States District Court for the District of Delaware [Novartis Pharmaceuticals, et. al. v. Alvogen Pine Brook, Inc., et. al., Civil Action Nos. 1:13-cv-00052-RGA (4.6 mg/24 hr and 9.5 mg/24 hr products) and 13-cv-0370 (13.3 mg/24 hr product)]. You have notified the Agency that the United States District Court for the District of Delaware determined that your 4.6 mg/24 hr and 9.5 mg/24 hr products do not infringe these patents. The same Court also entered a Joint Stipulation of Dismissal for the 13.3 mg product.

However, we are unable to grant final approval to your ANDA at this time. You have notified the agency that you will not market your ANDA until the expiration of the new strength (NS) exclusivity that is associated with Exelon Transdermal System, 13.3 mg/24 hr. Therefore, final approval of your ANDA may not be made effective pursuant to section 505(j)(5)(F)(iv) of the FD&C Act prior to the expiration of the exclusivity on August 31, 2015.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

To reactivate your ANDA prior to final approval, please submit a “MINOR AMENDMENT – FINAL APPROVAL REQUESTED” 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, or a settlement or licensing agreement, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT – FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' cGMPs are subject to agency review before final approval of the ANDA will be made. Such changes should be categorized as representing either “major” or “minor” changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the FD&C Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the FD&C Act. Also, until the agency issues the final approval letter, this drug product will not be deemed to be

approved for marketing under section 505 of the FD&C Act, and will not be listed in the “Orange Book.”

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

For further information on the status of this ANDA, or prior to submitting additional amendments, please contact Andrew Potter, Regulatory Project Manager, at 240-402-9266.

Sincerely yours,

**William P.
Rickman -S**

For Carol A. Holquist, RPh
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Digitally signed by William P. Rickman -S
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0.9.2342.19200300.100.1.1=1300043242,
cn=William P. Rickman -S
Date: 2015.07.22 14:56:01 -04'00'

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 204403

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **Rivastigmine Patch** safely and effectively. See full prescribing information for **Rivastigmine Patch**.

RIVASTIGMINE transdermal system

Initial U.S. Approval: 2000

RECENT MAJOR CHANGES

Dosage and Administration (2.2, 2.4) 01/2015
Warnings and Precautions (5.1, 5.3) 01/2015

INDICATIONS AND USAGE

Rivastigmine Patch is an acetylcholinesterase inhibitor indicated for treatment of:

- Mild to moderate dementia of the Alzheimer's type (1.1)
- Mild to moderate dementia associated with Parkinson's disease (1.2)

DOSEAGE AND ADMINISTRATION

- Apply patch on intact skin for a 24-hour period; replace with a new patch every 24 hours. (2.1, 2.4)
- Initiate treatment with 4.6 mg/24 hours Rivastigmine Patch (2.1)
- After a minimum of 4 weeks, if tolerated, increase dose to 9.5 mg/24 hours, which is the minimum effective dose (2.1)
- Following a minimum additional 4 weeks, may increase dosage to maximum dosage of 13.3 mg/24 hours (2.1)
- Mild to Moderate Alzheimer's Disease and Parkinson's Disease Dementia: Rivastigmine Patch 9.5 mg/24 hours or 13.3 mg/24 hours once daily (2.1)
- For treatment interruption longer than three days, retreat dosage starting at 4.6 mg/24 hours. (2.1)
- Consider dose adjustments in patients with (2.2):
 - Mild to moderate hepatic impairment (8.6)
 - Low (<50 kg) body weight (8.7)

DOSEAGE FORMS AND STRENGTHS

Patch: 4.6 mg/24 hours or 9.5 mg/24 hours or 13.3 mg/24 hours (3)

CONTRAINDICATIONS

- Known hypersensitivity to rivastigmine, other carbamate derivatives, or other components of the formulation. (4)
- History of application site reactions with rivastigmine transdermal patch suggestive of allergic contact dermatitis. (4, 6.2)

WARNINGS AND PRECAUTIONS

- Hospitalization and, rarely, death have been reported due to application of multiple patches at same time. Ensure patients or caregivers receive instruction on proper dosing and administration. (5.1)

- Gastrointestinal adverse reactions: May include significant nausea, vomiting, diarrhea, anorexia/decreased appetite, and weight loss, and may necessitate treatment interruption. Dehydration may result from prolonged vomiting or diarrhea and can be associated with serious outcomes. (5.2)

- Application site reactions may occur with the patch form of rivastigmine. Discontinue treatment if application site reactions spread beyond the patch site. If there is evidence of a more intense local reaction (e.g., increasing erythema, edema, papules, vesicles), and if symptoms do not significantly improve within 48 hours after patch removal. (5.3)
- MRI skin burns: Skin burns have been reported in patients undergoing MRI testing. (5.6)

ADVERSE REACTIONS

Most common adverse reactions (>5% and higher than with placebo): Nausea, vomiting, and diarrhea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alvoigen Customer Service at 1-866-770-3024 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Concomitant use with metoprolamide, beta-blockers, or cholinomimetics and anticholinergic medications is not recommended. (7.1, 7.2, 7.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 06/2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Alzheimer's Disease

Rivastigmine Patch is indicated for the treatment of dementia of the Alzheimer's type (AD). Efficacy has been demonstrated in patients with mild to moderate Alzheimer's disease.

1.2 Parkinson's Disease Dementia

Rivastigmine Patch is indicated for the treatment of mild to moderate dementia associated with Parkinson's disease (PDD).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Initiate treatment with one 4.6 mg/24 hours Rivastigmine Patch applied to the skin once daily [see *Dosage and Administration* (2.4)].

Dose Titration

Increase the dose only after a minimum of 4 weeks at the previous dose, and only if the previous dose has been tolerated. For mild to moderate AD and PDD patients, continue the effective dose of 9.5 mg/24 hours for as long as therapeutic benefit persists. Patients can then be increased to the maximum effective dose of 13.3 mg/24 hours. Doses higher than 13.3 mg/24 hours confer no appreciable additional benefit, and are associated with an increase in the incidence of adverse reactions [see *Warnings and Precautions* (5.2), *Adverse Reactions* (6.1)].

Mild to Moderate Alzheimer's Disease and Mild to Moderate Parkinson's Disease Dementia

The effective dosage of Rivastigmine Patch is 9.5 mg/24 hours or 13.3 mg/24 hours administered once per day; replace with a new patch every 24 hours.

Interruption of Treatment

If dosing is interrupted for 3 days or fewer, restart treatment with the same or lower strength Rivastigmine Patch. If dosing is interrupted for more than 3 days, restart treatment with the 4.6 mg/24 hours Rivastigmine Patch and titrate as described above.

2.2 Dosing in Specific Populations

Consider using the 4.6 mg/24 hours Rivastigmine Patch as both the initial and maintenance dose in patients with mild (Child-Pugh score 5 to 6) to moderate (Child-Pugh score 7 to 9) hepatic impairment [see *Use in Specific Populations* (8.6) and *Clinical Pharmacology* (12.3)].

Dosing Modifications in Patients with Low Body Weight

Cautionly titrate and monitor patients with low body weight (<50 kg) for toxicities (e.g., excessive nausea, vomiting) and consider reducing the maintenance dose to the 4.6 mg/24 hours Rivastigmine Patch if such toxicities develop.

2.3 Switching to Rivastigmine Patch from Rivastigmine Capsules or Rivastigmine Oral Solution

Patients treated with rivastigmine capsules or oral solution may be switched to Rivastigmine Patch as follows:

- A patient who is on a total daily dose of <6 mg of oral rivastigmine can be switched to the 4.6 mg/24 hours Rivastigmine Patch.

- A patient who is on a total daily dose of 6 mg to 12 mg of oral rivastigmine can be switched to the 9.5 mg/24 hours Rivastigmine Patch.

Instruct patients or caregivers to apply the first patch on the day following the last oral dose.

2.4 Important Administration Instructions

Rivastigmine Patch is for transdermal use on intact skin.

(a) Do not use the patch if the pouch seal is broken or the patch is cut, damaged, or changed in any way.

(b) Apply the Rivastigmine Patch once a day

- Press down firmly for 30 seconds until the edges stick well when applying to clean, dry, hairless, intact healthy skin in a place that will not be rubbed against by tight clothing.

- Use the upper or lower back as the site of application because the patch is less likely to be removed by the patient. If sites on the back are not accessible, apply the patch to the upper arm or chest.

- Do not apply to a skin area where cream, lotion, or powder has recently been applied.

(c) Do not apply to skin that is red, irritated, or cut.

(d) Replace the Rivastigmine Patch with a new patch every 24 hours. Instruct patients to only wear one patch at a time (remove the previous day's patch before applying a new patch) [see *Warnings and Precautions* (5.1) and *Overdosage* (10)]. If a patch falls off or if a dose is missed, apply a new patch immediately and then replace this patch the following day at the usual application time.

(e) Change the site of patch application daily to minimize potential irritation, although a new patch can be applied to the same general anatomic site (e.g., another spot on the upper back) on consecutive days. Do not apply a new patch to the same location for at least 14 days.

(f) May wear the patch during bathing and in hot weather. But avoid long exposure to external heat sources (excessive sunlight, saunas, solariums).

(g) Place used patches in the previously saved pouch and discard in the trash, away from pets or children.

(h) Wash hands with soap and water after removing the patch. In case of contact with eyes or if the eyes become red after handling the patch, rinse immediately with plenty of water and seek medical advice if symptoms do not resolve.

3 DOSAGE FORMS AND STRENGTHS

Rivastigmine Patch is available in 3 strengths. Each patch has a tan backing layer labeled as either:

- Rivastigmine Patch 4.6 mg/24 hours, "RIV-TDS 4.6 mg/24 h"
- Rivastigmine Patch 9.5 mg/24 hours, "RIV-TDS 9.5 mg/24 h"
- Rivastigmine Patch 13.3 mg/24 hours, "RIV-TDS 13.3 mg/24 h"

4 CONTRAINDICATIONS

Rivastigmine Patch is contraindicated in patients with:

- known hypersensitivity to rivastigmine, other carbamate derivatives, or other components of the formulation [see *Description* (11)].

- previous history of application site reactions with rivastigmine transdermal patch suggestive of allergic contact dermatitis [see *Warnings and Precautions* (5.3)].

Isolated cases of generalized skin reactions have been described in postmarketing experience [see *Adverse Reactions* (6.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Medication Errors Resulting in Overdose

Medication errors with Rivastigmine Patch have resulted in serious adverse reactions: some cases have required hospitalization, and rarely, led to death. The majority of medication errors have involved not removing the old patch when putting on a new one and the use of multiple patches at one time.

Instruct patients and their caregivers on important administration instructions for Rivastigmine Patch [see *Dosage and Administration* (2.4)].

5.2 Gastrointestinal Adverse Reactions

Rivastigmine Patch can cause gastrointestinal adverse reactions, including significant nausea, vomiting, diarrhea, anorexia/decreased appetite, and weight loss. Dehydration may result from prolonged vomiting or diarrhea and can be associated with serious outcomes. The incidence and severity of these reactions are dose-related [see *Adverse Reactions* (6.1)]. For this reason, initiate treatment with Rivastigmine Patch at a dose of 4.6 mg/24 hours and titrate to a dose of 9.5 mg/24 hours and then to a dose of 13.3 mg/24 hours, if appropriate [see *Dosage and Administration* (2.1)].

If treatment is interrupted for more than 3 days because of intolerance, reinstitute Rivastigmine Patch with the 4.6 mg/24 hours dose to reduce the possibility of severe vomiting and its potentially serious sequelae. A postmarketing report described a case of severe vomiting with esophageal rupture following inappropriate reinitiation of treatment of oral formulation of rivastigmine without retreatment after 8 weeks of treatment interruption.

Inform caregivers to monitor for gastrointestinal adverse reactions and to inform the physician if they occur. It is critical to inform caregivers that if therapy has been interrupted for more than 3 days because of intolerance, the next dose should not be administered without contacting the physician regarding proper retreatment.

5.3 Skin Reactions

Skin application site reactions may occur with Rivastigmine Patch. These reactions are not limited to application site sensitization. However, use of rivastigmine patch may lead to allergic contact dermatitis.

Allergic contact dermatitis should be suspected if application site reactions spread beyond the patch size. If there is evidence of a more intense local reaction (e.g., increasing erythema, edema, papules, vesicles) and if symptoms do not significantly improve within 48 hours after patch removal. In these cases, treatment should be discontinued [see *Contraindications* (4)].

In patients who develop application site reactions to Rivastigmine Patch suggestive of allergic contact dermatitis and who are unable to discontinue treatment, treatment should be switched to oral rivastigmine only after negative allergy testing and under close medical supervision. It is possible that some patients sensitized to rivastigmine by exposure to rivastigmine patch may not be able to take rivastigmine in any form.

There have been isolated postmarketing reports of patients experiencing disseminated allergic dermatitis when administered rivastigmine irrespective of the route of administration (oral, transdermal, and intravenous) [see *Contraindications* (4)]. Patients and caregivers should be instructed accordingly.

5.4 Other Adverse Reactions from Increased Cholinergic Activity

Extrapyramidal Symptoms: Cholinomimetics, including rivastigmine may exacerbate or induce extrapyramidal symptoms. Worsening of parkinsonian symptoms, particularly tremor, has been observed in patients with dementia associated with Parkinson's disease who were treated with rivastigmine capsules.

Seizures: Drugs that increase cholinergic activity are believed to have some potential for causing seizures. However, seizure activity also may be a manifestation of Alzheimer's disease.

Psychic Effects/Gastrointestinal Bleeding:

Cholinesterase inhibitors, including rivastigmine, may increase gastric acid secretion due to increased cholinergic activity. Monitor patients using rivastigmine Patch for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs). Clinical studies of rivastigmine have shown no significant increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Use with Anesthesia

Rivastigmine, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Cardiac Conduction Effects

Because rivastigmine increases cholinergic activity, use of the Rivastigmine Patch may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be exaggerated in patients with sick sinus syndrome or other supraventricular cardiac conduction conditions. In clinical trials, rivastigmine was not associated with any increased incidence of cardiovascular adverse events, heart rate or blood pressure changes, or ECG abnormalities.

Gonorrheal Effects

Although not observed in clinical trials of rivastigmine, drugs that increase cholinergic activity may cause urinary obstruction.

Pulmonary Effects

Drugs that increase cholinergic activity, including Rivastigmine Patch should be used with care in patients with a history of asthma or severe pulmonary disease.

5.5 Impairment in Driving or Use of Machinery

Dementia may impair judgment or impairment of driving performance or compromise the ability to use machinery. The administration of rivastigmine may also result in adverse reactions that are detrimental to these functions. During treatment with the Rivastigmine Patch, routinely evaluate the patient's ability to continue driving or operating machinery.

5.6 MRI Skin Burns

Skin burns have been reported at the patch site in several patients wearing an aluminumized transdermal system during a Magnetic Resonance Imaging scan (MRI). Because the Rivastigmine Patch contains aluminum, it is recommended to remove the system before undergoing an MRI.

6 ADVERSE REACTIONS

The following adverse reactions are described below and elsewhere in the labeling:

- Gastrointestinal Adverse Reactions [see *Warnings and Precautions* (5.2)].
- Skin Reactions [see *Warnings and Precautions* (5.3)].
- Other Adverse Reactions from Increased Cholinergic Activity [see *Warnings and Precautions* (5.4)].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Rivastigmine Patch has been administered to 4516 patients with Alzheimer's disease during clinical trials worldwide. Of these, 3005 patients have been treated for at least 26 weeks, 1771 patients have been treated for at least 52 weeks, 974 patients have been treated for at least 78 weeks and 24 patients have been treated for at least 104 weeks.

Mild to Moderate Alzheimer's Disease

24-Week International Placebo-Controlled Trial (Study 1)

Most Common Adverse Reactions

The most common adverse reactions in patients administered Rivastigmine Patch in Study 1 [see *Clinical Studies* (14)], defined as those occurring at a frequency of at least 5% in the 9.5 mg/24 hours Rivastigmine Patch arm and at a frequency at higher than in the placebo group, were nausea, vomiting, and diarrhea. These reactions were dose-related, with each being more common in patients using the unapproved 17.4 mg/24 hours Rivastigmine Patch than in those using the 9.5 mg/24 hours Rivastigmine Patch.

Discontinuation Rates

In Study 1, which randomized a total of 1195 patients, the proportions of patients in the Rivastigmine Patch 9.5 mg/24 hours, rivastigmine capsules 6 mg twice daily, and placebo groups, respectively. The proportions of patients who discontinued treatment due to vomiting were 0%, 2.0%, and 0.3% in the Rivastigmine Patch 9.5 mg/24 hours, rivastigmine capsules 6 mg twice daily, and placebo groups, respectively.

Adverse Reactions Observed at an Incidence of <2%

Table 1 lists adverse reactions seen at an incidence of <2% in either Rivastigmine Patch-treated group in Study 1 and for which the rate of occurrence was greater for patients treated with that dose of Rivastigmine Patch than for those treated with placebo. The unapproved 17.4 mg/24 hours Rivastigmine Patch arm is included to demonstrate the increased rates of gastrointestinal adverse reactions over those seen with the 9.5 mg/24 hours Rivastigmine Patch.

Table 1: Proportion of Adverse Reactions Observed with a Frequency of $\geq$ 2% and Occurring at a Rate Greater Than Placebo in Study 1

	Rivastigmine Patch 9.5 mg/ 24 hours	Rivastigmine Patch 17.4 mg/ 24 hours	Rivastigmine capsule 6 mg twice daily	Placebo
Total Patients Studied	291	303	294	302
Total Percentage of Patients Studied with AEs (%)	51	66	63	46
Nausea	7	21	23	5
Vomiting**	6	19	17	3
Diarrhea	6	10	5	3
Depression	4	4	4	1
Headache	3	4	6	2
Anxiety	3	3	2	1
Anorexia/Decreased Appetite	3	9	9	2
Weight Decreased**	3	8	5	1
Dizziness	2	7	7	2
Abdominal Pain	2	4	1	1
Urinary Tract Infection	2	2	1	1
Asthma	2	3	6	1
Fatigue	2	2	1	1
Insomnia	1	4	2	2
Abdominal Pain Upper	1	3	2	2
Vertigo	0	2	1	1

*Vomiting was severe in 0% of patients who received Rivastigmine Patch 9.5 mg/24 hours, 1% of patients who received Rivastigmine Patch 17.4 mg/24 hours, and 0% of those who received placebo.

**Weight decreased as presented in Table 1 is based upon clinical observations and/or adverse events reported by patients or caregivers. Body weight was also monitored at prespecified time points throughout the course of the clinical study. The proportion of patients who had weight loss equal to or greater than 7% of their baseline weight was 8% of those treated with Rivastigmine Patch 9.5 mg/24 hours, 12% of those treated with Rivastigmine Patch 17.4 mg/24 hours, 11% of patients who received the rivastigmine capsule at doses up to 6 mg twice daily and 6% of those who received placebo. It is not clear how much of the weight loss was associated with anorexia, nausea, vomiting, and the diarrhea associated with the drug.

48-Week International Active-Controlled Trial (Study 2)

Most Common Adverse Reactions

In Study 2 [see *Clinical Studies* (14)] of the commonly observed adverse reactions (>3% in any treatment group) the most frequent events in the Rivastigmine Patch 13.3 mg/24 hours group were nausea, followed by vomiting, fall, weight decreased, application site erythema, decreased appetite, diarrhea and urinary tract infection (Table 3). The percentage of patients with these events was higher in the Rivastigmine Patch 13.3 mg/24 hours group than in the Rivastigmine Patch 9.5 mg/24 hours group. Patients with nausea, vomiting, diarrhea and decreased appetite experienced these reactions more often during the first 4 weeks of the double-blind treatment phase. These reactions decreased over time in each treatment group. Weight decreased was reported to have increased over time in each treatment group.

Discontinuation Rates

Table 2 displays the most common adverse reactions leading to discontinuation during the 48-week, double-blind treatment phase in Study 2.

Table 2: Proportion of Most Common Adverse Reactions (>1% at Any Dose) Leading to Discontinuation During 48-week Double-Blind Treatment Phase in Study 2

	Rivastigmine Patch 13.3 mg/24 hours	Rivastigmine Patch 9.5 mg/24 hours	Total
Total Patients Studied	280	283	563
Total Percentage of Patients with AEs Leading to Discontinuation (%)	9.6	12.7	11.2
Vomiting	1.4	0.4	0.9
Application site pruritus	1.1	1.1	1.1
Aggression	0.4	1.1	0.7

Most Common Adverse Reactions >3%

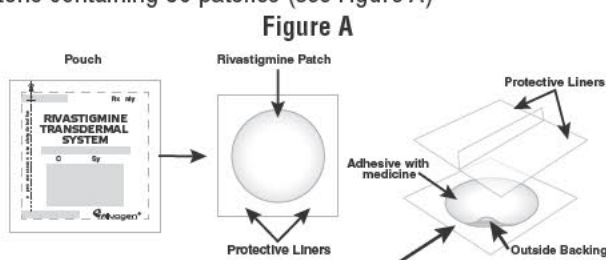
Other adverse reactions of interest which occurred less frequently, but which were observed in a markedly higher percentage of patients in the Rivastigmine Patch 13.3 mg/24 hours group than in the Rivastigmine Patch 9.5 mg/24 hours group in Study 2, included dizziness and upper abdominal pain. The percentage of patients with these reactions decreased over time in each treatment group (Table 3). The adverse reaction weight loss was generally similar for both the Rivastigmine Patch 13.3 mg/24 hours and 9.5 mg/24 hours groups.

Table 3: Proportion of Adverse Reactions Over Time in the 48-week Double-Blind (DB) Treatment Phase (at Least 3% in Any Treatment Group) in Study 2

	Cumulative Week 0 to 48 (DB Phase)	Week 0 to 24 (DB Phase)	Week >24 to 48 (DB Phase)			
Total Patients Studied	280	283	241	246		
Total Percentage of Patients with AEs Leading to Discontinuation (%)	75	68	65	55	42	40
Nausea	12	5	10	4	4	2
Vomiting	10	5	9	3	3	2
Fall	8	6	4	4	4	3
Weight decreased*	7	3	3	1	5	2
Application site erythema	6	6	6	5	1	2
Decreased appetite	6	3	5	2	2	<1
Diarrhea	6	5	5	4	2	<1
Urinary tract infection	5	4	3	3	3	2
Agtitation	5	5	4	3	1	2
Depression	5	5	3	3	3	2
Dizziness	4	1	3	<1	2	<1
Aggression	4	4	4	3	<1	<1
Headache	4	4	4	4	<1	<1
Insomnia	4	3	2	1	3	2

Instructions for Use Rivastigmine (riv[®] a stig[®] meen) Patch (rivastigmine transdermal system)

You will need the following supplies (See Figure A):
Rivastigmine Patch is supplied in cartons containing 30 patches (See Figure A)

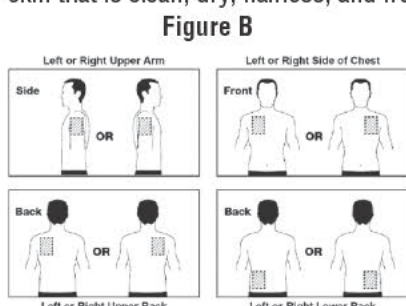


- Rivastigmine Patch is a thin, tan, plastic patch that sticks to the skin. Each Rivastigmine Patch is sealed in a pouch that protects it until you are ready to put it on. (See Figure A).
- Only 1 Rivastigmine Patch should be worn at a time. Do not apply more than 1 Rivastigmine Patch at a time to the body.
- Do not open the pouch or remove the Rivastigmine Patch until you are ready to apply it.

Using Rivastigmine Patch:

Step 1. Choose an area to apply the Rivastigmine Patch (See Figure B).

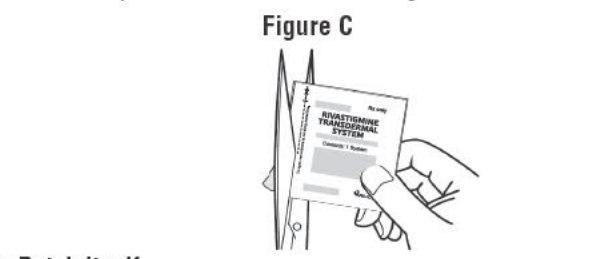
- Instructions for Caregivers: Apply Rivastigmine Patch to the upper or lower back if it is likely that the patient will remove it. If this is not a concern, the Rivastigmine Patch can be applied instead to the upper arm or chest. Do not apply the Rivastigmine Patch to areas where it can be rubbed off by tight clothing or belts.
- Only apply the Rivastigmine Patch to healthy skin that is clean, dry, hairless, and free of redness, irritation, burns or cuts.



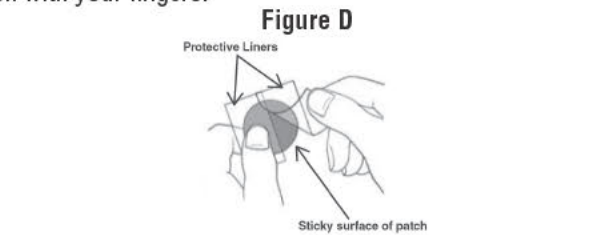
The diagram represents areas on the body where Rivastigmine Patch may be applied. Only 1 patch should be worn at a time. Do not apply multiple patches to the body.

Step 2. Remove the Rivastigmine Patch from the pouch (See Figure C).

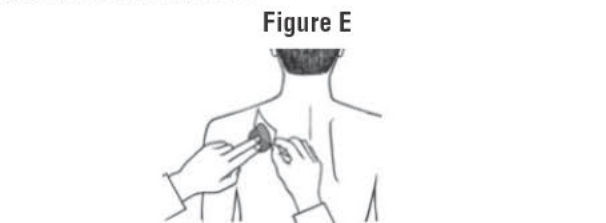
Carefully cut the pouch along the dotted line to open and remove the Rivastigmine Patch. Save the pouch for later use.



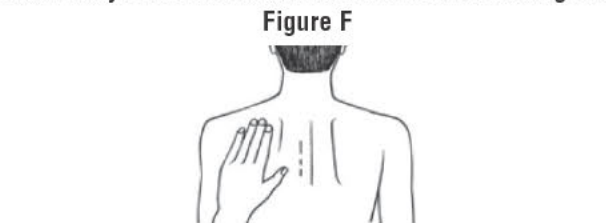
- Do not cut or fold the Rivastigmine Patch itself.
- Step 3. Remove 1 side of the adhesive liner (See Figure D).
- A protective liner covers the sticky (adhesive) side of the Rivastigmine Patch. Peel off 1 side of the protective liner. Do not touch the sticky part of the Rivastigmine Patch with your fingers.



- Step 4. Apply the Rivastigmine Patch to your skin (See Figure E).
- Apply the sticky (adhesive) side of the Rivastigmine Patch onto your chosen area of skin and then peel off the other side of the protective liner as well as the cover sheet and discard both.



- Press down on the Rivastigmine Patch firmly for 30 seconds to make sure that the edges stick to your skin (See Figure F).



Step 5: Wash your hands with soap and water right away.

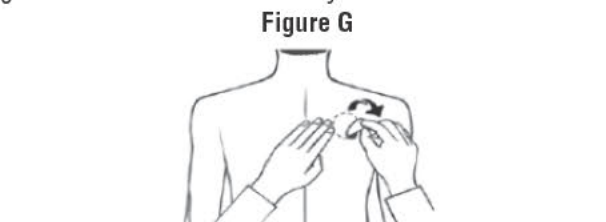
Note:

- If your Rivastigmine Patch falls off, select a new area, and repeat Steps 2 to 5 to apply a new Rivastigmine Patch.
- Be sure to replace the new Rivastigmine Patch the next day at the same time as usual.

Removing the Rivastigmine Patch:

Step 6. Remove the Rivastigmine Patch from the skin (See Figure G).

- Gently pull on 1 edge of the Rivastigmine Patch to remove it from your skin.



Throwing away the used Rivastigmine Patch:

Step 7. Throw away the used Rivastigmine Patch (See Figure H).

- Fold the Rivastigmine Patch in half (with the sticky sides together) and put it back into the pouch that you saved.



- Throw away the used Rivastigmine Patch safely out of the reach of children and pets.
- Some medicine stays in the patch for 24 hours after you use it and should be folded together (sticky side together) and safely thrown away. Do not try to re-use Rivastigmine Patches.

Step 8: Wash your hands with soap and water right away.

- After you remove the Rivastigmine patch, if any adhesive remains on your skin, you can use soap and water or an oil-based substance (such as baby oil) to remove the adhesive. Alcohol or other dissolving liquids (such as nail polish remover) should not be used.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Made in Germany
Distributed by:
Alvogen, Inc.
Pine Brook, NJ 07058 USA
PL304-02

06/2015

Table 4. Continued

Preferred term	Rivastigmine Patch 13.3 mg/24 hours	Rivastigmine Patch 4.6 mg/24 hours
Total number of patients studied	355	359
Total percentage of patients with AEs (%)	75	75
Diarrhea	7	5
Weight decreased*	7	3
Nausea	6	3
Depression	5	4
Loss of appetite	5	1
Anxiety	5	5
Hallucination	2	5

*Weight Decreased as presented in Table 4 is based upon clinical observations and/or adverse events reported by patients or caregivers. Body weight was monitored as a vital sign at pre-specified time points throughout the course of the clinical study. The proportion of patients who had weight loss equal to or greater than 7% of their baseline weight was 11% of those treated with Rivastigmine Patch 4.6 mg/24 hours and 14.1% of those treated with Rivastigmine Patch 13.3 mg/24 hours during the 24-week double-blind treatment.

Application Site Reactions

Application site skin reactions leading to discontinuation were observed in $\leq 2.3\%$ of Rivastigmine Patch patients. This number was 4.9% and 8.4% in the Chinese population and Japanese population, respectively. Cases of skin irritation were captured separately on an investigator-rated skin irritation scale. Skin irritation, when observed, was mostly slight or mild in severity and was rated as severe in $\leq 2.2\%$ of Rivastigmine Patch patients in a double-blind controlled study and in $\leq 3.7\%$ of Rivastigmine Patch patients in a double-blind controlled study in Japanese patients.

Parkinson's Disease Dementia

76-week International Open Label Trial (Study 4)
Rivastigmine Patch has been administered to 288 patients with mild to moderate Parkinson's Disease Dementia in a single, 76-week, open-label, active-comparator safety study. Of these, 256 have been treated for at least 12 weeks, 232 for at least 24 weeks, and 190 for at least 52 weeks.

Treatment with Rivastigmine patch was initiated at 4.6 mg/24 hours and it tolerated the dose was increased after 4 weeks to 9.5 mg/24 hours. Rivastigmine capsule (target maintenance dose of 12 mg/day) served as the active comparator and was administered to 294 patients. Adverse reactions are presented in Table 5.

Table 5. Proportion of Adverse Reactions Reported at a Rate $\geq 2\%$ During the Initial 24-Week Period in Study 4

Adverse drug reactions	Rivastigmine Patch
	Percentage (%)
Psychiatric disorders	
Insomnia	6
Depression	6
Anxiety	6
Agitation	5
Nervous system disorders	
Tremor	7
Dizziness	6
Somnolence	6
Hypokinetic	4
Headache	4
Cogwheel rigidity	3
Dyskinesia	3
Gastrointestinal disorders	
Abdominal pain	2
Vascular disorders	
Hypertension	3
General disorders and administration site conditions	
Fatigue	12
Application site erythema	11
Application site irritation, pruritus, rash	3; 5; 2
Fatigue	4
Asthenia	2
Gait disturbance	4

Additional adverse reactions observed during the 76-week prospective, open-label study in patients with dementia associated with Parkinson's disease treated with Rivastigmine patches: Frequent (those occurring in at least 1/100 patients); dehydration, weight decreased, aggression, hallucination visual.

In patients with dementia associated with Parkinson's disease the following adverse drug reactions have only been observed in clinical trials with rivastigmine capsules: frequent, nausea, vomiting, decreased appetite, restlessness, worsening of Parkinson's disease, bradycardia, diarrhea, dyspepsia, salivary hypersecretion, sweating increased, inpatient infection between 1/100 to 1/1000 patients), dystonia, atrial fibrillation, atrioventricular block.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of rivastigmine. Because these reactions were reported from a variety of sources of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypertension, application site hypersensitivity, urticaria, allergic dermatitis, dermatitis, Parkinson's disease (worsening), tachycardia, abnormal liver function tests, disseminated allergic dermatitis, and tremor.

7 DRUG INTERACTIONS

7.1 Metoclopramide

Due to the risk of additive extra-pyramidal adverse reactions, the concomitant use of metoclopramide and rivastigmine is not recommended.

7.2 Cholinergic and Anticholinergic Medications

Rivastigmine Patch may increase the cholinergic effects of other cholinergic medications and may also interfere with the activity of anticholinergic medications (e.g., oxybutynin, tolterodine). Concomitant use of Rivastigmine Patch with medications having these pharmacologic effects is not recommended unless deemed clinically necessary (see Warnings and Precautions (5.4)).

7.3 Beta-blockers

Additive bradycardic effects resulting in syncope may occur when rivastigmine is used concomitantly with beta-blockers, especially beta-blockers (including atenolol). Concomitant use is not recommended when signs of bradycardia including syncope are present.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B
There are no adequate and well-controlled studies in pregnant women. No dermal reproduction studies in animals have been conducted.

Oral reproduction studies conducted in pregnant rats and rabbits revealed no evidence of teratogenicity. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.2 Lactation

8.3 Nursing Mothers
Rivastigmine and its metabolites are excreted in rat milk following oral administration of rivastigmine. Levels of rivastigmine plus metabolites in rat milk are approximately 2 times that in maternal plasma. It is not known whether rivastigmine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Rivastigmine Patch, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Use of Rivastigmine Patch in pediatric patients (below 18 years of age) is not recommended.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Rivastigmine Patch, 88% were 65 and over, while 55% were 75 years. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experiences has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

Increased exposure to rivastigmine was observed in patients with mild or moderate hepatic impairment with oral rivastigmine. Patients with mild or moderate hepatic impairment may be able to only tolerate lower doses (see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)). No data are available on the use of rivastigmine in patients with severe hepatic impairment.

8.7 Low or High Body Weight

Because rivastigmine blood levels vary with weight, careful titration and monitoring should be performed in patients with low or high body weights (see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)).

10 OVERDOSAGE

Overdose with Rivastigmine Patch has been reported in the postmarketing setting (see Warnings and Precautions (5.1)). Overdoses have occurred from application of more than one patch at one time and removal of the previous day's patch before applying a new patch. The symptoms reported in these overdose cases are similar to those seen in cases of overdose associated with rivastigmine oral formulations.

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug. As rivastigmine has a plasma half-life of about 3.4 hours after patch administration and a duration of acetylcholinesterase inhibition of about 9 hours, it is recommended that in cases of asymptomatic overdose the patch should be immediately removed and no further patch should be applied for the next 24 hours.

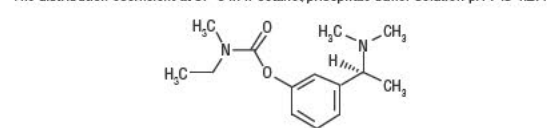
As in any case of overdose, general supportive measures should be utilized. Overdose with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Atypical responses in blood pressure and heart rate have been reported with other drugs that increase cholinergic activity when administered with quaternary anticholinergics such as glycopyrrolate. Additional symptoms associated with rivastigmine overdose are diarrhea, abdominal pain, dizziness, tremor, headache, somnolence, confusion, hyperhidrosis, hypertension, hallucinations and malaise. Due to the short plasma elimination half-life of rivastigmine after patch administration, dialysis (hemodialysis, peritoneal dialysis, or hemofiltration) would not be clinically indicated in the event of an overdose.

In overdose accompanied by severe nausea and vomiting, the use of antiemetics should be considered. A fatal outcome has rarely been reported with rivastigmine overdose.

11 DESCRIPTION

Rivastigmine Patch (rivastigmine transdermal system) contains rivastigmine, a reversible cholinesterase inhibitor known chemically as (S)-3-[(1-dimethylamino) ethyl] phenyl ethylmethylcarbamate. It has an empirical formula of $C_{16}H_{21}N_2O_3$ as the base and a molecular weight of 290.34 (as the base). Rivastigmine is a viscous, clear, and colorless to yellow to very slightly brown liquid that is sparingly soluble in water and very soluble in ethanol, acetonitrile, n-octanol and ethyl acetate.

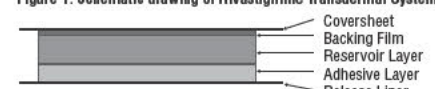
The distribution coefficient at 37°C in n-octanol/phosphate buffer solution pH 7 is 4.27.



Rivastigmine Patch is for transdermal administration. The patch comprises a multi-layer laminate containing the cover sheet, backing film, reservoir layer, adhesive layer, and release liner as described below. The release liner is removed and discarded prior to use. See Figure 1 for a detailed illustration.

- cover sheet: siliconized polyethylene terephthalate film
- backing film: Polyethylene / thermoplastic resin / aluminum coated polyester film
- an active reservoir layer containing the active pharmaceutical ingredient
- an adhesive matrix layer
- release liner: fluoropolymer coated polyester film

Figure 1. Schematic drawing of Rivastigmine Transdermal System



Excipients within the formulation include colloidal silicon dioxide, light mineral oil, polybutylene adhesive, acrylic-vinylacetate pressure sensitive adhesive, aluminum coated polyester backing.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Although the precise mechanism of action of rivastigmine is unknown, it is thought to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. The effect of rivastigmine may be lessened as the disease progresses and fewer cholinergic neurons remain functionally intact. There is no evidence that rivastigmine alters the course of the underlying dementing process.

12.2 Pharmacodynamics

After a 6-mg oral dose of rivastigmine in humans, anticholinesterase activity is present in cerebrospinal fluid for about 10 hours, with a maximum inhibition of about 60% 5 hours after dosing.

In vitro and *in vivo* studies demonstrate that the inhibition of cholinesterase by rivastigmine is not affected by the concomitant administration of memantine, an N-methyl-D-aspartate receptor antagonist.

12.3 Pharmacokinetics

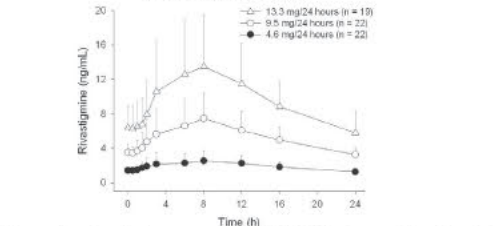
Absorption

After the initial application of Rivastigmine Patch, there is a lag time of 0.5 to 1 hour in the absorption of rivastigmine. Concentrations then rise slowly typically reaching a maximum after 8 hours, although maximum values (C_{max}) can also occur later (at 10 to 16 hours). After the peak, plasma concentrations slowly decrease over the remainder of the 24-hour period of application. At steady state, trough levels are approximately 60% to 80% of peak levels.

Rivastigmine Patch 9.5 mg/24 hours gave exposure approximately the same as that provided by an oral dose of 6 mg twice daily (i.e., 12 mg/day). Inter-subject variability in exposure (AUC) is 45% to 46% for the Rivastigmine Patch formulation as compared with the oral formulations (73% to 103%). Fluctuation (between C_{max} and C_{min}) is less for Rivastigmine Patch than for the oral formulation of rivastigmine.

Figure 2 displays rivastigmine plasma concentrations over 24 hours for the 3 available patch strengths.

Figure 2. Rivastigmine Plasma Concentrations Following Dermal 24-Hour Patch Application



Over a 24-hour dermal application, approximately 50% of the drug content of the patch is released from the system.

Exposure (AUC₀₋₂₄) to rivastigmine (and metabolite NAP266-90) was highest when the patch was applied to the upper back, chest, or upper arm. Two other sites (abdomen and thigh) could be used if none of the three other sites is available, but the practitioner should be aware that the rivastigmine plasma exposure associated with these sites was approximately 20 to 30% that of the other sites.

There was no relevant accumulation of rivastigmine or the metabolite NAP266-90 in plasma in patients with Alzheimer's disease with daily dosing.

The pharmacokinetic profile of rivastigmine transdermal patches was comparable in patients with Alzheimer's disease and in patients with dementia associated with Parkinson's disease.

Distribution

Rivastigmine is weakly bound to plasma proteins (approximately 40%) over the therapeutic range. It readily crosses the blood-brain barrier, reaching CSF peak concentrations in 1.5 to 2 hours. It has an apparent volume of distribution in the range of 1.8 to 2.7 L/kg.

Metabolism

Rivastigmine is extensively metabolized primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite NAP266-90. *In vitro*, this metabolite shows minimal inhibition of acetylcholinesterase (<10%). Based on evidence from *in vitro* and animal studies, the major cytochrome P450 isoenzymes are minimally involved in rivastigmine metabolism.

The metabolite-to-parent AUC₀₋₂₄ ratio was about 0.7 after Rivastigmine Patch application versus 3.5 after oral administration, indicating that much less metabolism occurred after dermal treatment. Less NAP266-90 is formed following patch application, presumably because of a decrease in presystemic (hepatic first pass) metabolism. Based on *in vivo* studies, no unique metabolic routes were detected in human skin.

Elimination

Renal excretion of the metabolites is the major route of elimination. Unchanged rivastigmine is found in trace amounts in the urine. Following administration of ¹⁴C-rivastigmine, renal elimination was rapid and essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the feces. The apparent elimination half-life in plasma is approximately 3 hours after patch removal. Renal clearance was approximately 2.1 to 2.8 L/hr.

Age

Age had no impact on the exposure to rivastigmine in Alzheimer's disease patients treated with Rivastigmine Patch.

Gender or Race

No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the disposition of Rivastigmine Patch. A population pharmacokinetic analysis of oral rivastigmine indicated that neither gender (n=277 males and 348 females) nor race (n=57 Caucasian, 34 Black, 4 Asian, and 12 Other) affected clearance of the drug. Similar results were seen with analyses of pharmacokinetic data obtained after the administration of Rivastigmine Patch.

Body Weight

A relationship between drug exposure at steady state (rivastigmine and metabolite NAP266-90) and body weight was observed in Alzheimer's dementia patients. Rivastigmine exposure is higher in subjects with low body weight. Compared to a patient with a body weight of 70 kg, the rivastigmine steady-state concentrations in a patient with a body weight of 35 kg would be approximately doubled, while for a patient with a body weight of 100 kg the concentrations would be approximately halved (see Dosage and Administration (2.2)).

Renal Impairment

No study was conducted with Rivastigmine Patch in subjects with renal impairment. Based on population analysis creatinine clearance did not show any clear effect on steady state concentrations of rivastigmine or its metabolite.

Hepatic Impairment

No pharmacokinetic study was conducted with Rivastigmine Patch in subjects with hepatic impairment. Following a single 3-mg dose, mean oral clearance of rivastigmine was 60% lower in hepatically impaired patients (n=10, biopsy proven) than in healthy subjects (n=10). After multiple 6-mg twice a day oral dosing, the mean clearance of rivastigmine was 65% lower in mild (n=7, Child-Pugh score 5 to 6) and moderate (n=3, Child-Pugh score 7 to 9) hepatically impaired patients (biopsy proven, liver cirrhosis) than in healthy subjects (n=10) (see Dosage and Administration (2.2), Clinical Populations (8.6)).

Smoking

Following oral rivastigmine administration (up to 12 mg/day) with nicotine use, the population pharmacokinetic analysis showed increased oral clearance of rivastigmine by 23% (n=75 smokers and 549 nonsmokers).

Drug Interaction Studies

No specific interaction studies have been conducted with Rivastigmine Patch. Information presented below is from studies with oral rivastigmine.

Effect of Rivastigmine on the Metabolism of Other Drugs

Rivastigmine is primarily metabolized through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Based on *in vitro* studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP1A2, CYP2B6, CYP2A6, CYP2C9, CYP2C8, CYP2C19, CYP2C10, or CYP2D6.

No pharmacokinetic interaction was observed between rivastigmine taken orally and digoxin, warfarin, diazepam or fluoxetine in studies in healthy volunteers. The increase in prothrombin time induced by warfarin is not affected by administration of rivastigmine.

Effect of Other Drugs on the Metabolism of Rivastigmine

Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine.

Population pharmacokinetic analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine taken orally were not influenced by commonly prescribed medications such as antiacids (n=7), antihypertensives (n=27), beta-blockers (n=42), calcium channel blockers (n=75), antidepressants (n=21), anti-inflammatory drugs (n=79), estrogens (n=70), salicylate analgesics (n=177), antidiabetics (n=35), and antihistamines (n=15).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
In oral carcinogenicity studies conducted at doses up to 1.1 mg base/kg/day in rats and 1.6 mg base/kg/day in mice, rivastigmine was not carcinogenic.

In a dermal carcinogenicity study conducted at doses up to 0.75 mg base/kg/day in mice, rivastigmine was not carcinogenic. The mean rivastigmine plasma exposure (AUC) at this dose was less than that in humans at the maximum recommended human dose (13.3 mg/24 hours).

Mutagenesis

Rivastigmine was clastogenic in *in vitro* chromosomal aberration assays in mammalian cells in the presence, but not the absence, of metabolic activation. Rivastigmine was negative in an *in vitro* bacterial reverse mutation (Ames) assay, an *in vitro* HGPRT assay, and in an *in vivo* mouse micronucleus test.

Impairment of Fertility

No fertility or reproduction studies of dermal rivastigmine have been conducted in animals. Rivastigmine had no effect on fertility or reproductive performance in rats at oral doses up to 1.1 mg base/kg/day.

14 CLINICAL STUDIES

The effectiveness of the Rivastigmine Patch in dementia of the Alzheimer's type and dementia associated with Parkinson's disease was based on the results of controlled trials of Rivastigmine Patch in patients with Alzheimer's disease (Studies 1 and 2) (see below); 3 controlled trials of oral rivastigmine in patients with dementia of the Alzheimer's type; and 1 controlled trial of oral rivastigmine in patients with dementia associated with Parkinson's disease. See the prescribing information for oral rivastigmine for details of the four studies of oral rivastigmine.

Mild to Moderate Alzheimer's Disease

International 24-Week Study of Rivastigmine Patch in Dementia of the Alzheimer's Type (Study 1)

This study was a randomized double-blind, double dummy clinical investigation in patients with Alzheimer's disease (diagnosed by NINCDS-ADRDA and DSM-IV criteria, Mini-Mental State Examination (MMSE) score ≥ 10 and ≤ 20) (Study 1). The mean age of patients participating in this trial was 74 years with a range of 50 to 90 years. Approximately 67% of patients were women, and 33% were men. The racial distribution was Caucasian 73%, Black 2%, Asian 9%, and other races 15%.

The effectiveness of the Rivastigmine Patch was evaluated in Study 1 using a dual outcome assessment strategy, evaluating for changes in both cognitive performance and overall clinical effect.

The ability of the Rivastigmine Patch to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's disease patients. The ADAS-Cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language, and praxis. The ADAS-Cog scoring range is from 0 to 70, with higher scores indicating greater cognitive impairment. In this study, mean scores were as low as 0 or 1, but it is not unusual for non-demented adults to score slightly higher.

The ability of the Rivastigmine Patch to produce an overall clinical effect was assessed using the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC). The ADAS-CGIC is a more standardized form of the Clinician's Interview-Based Impression of Change-Plus (CIBIC-Plus) and is also scored as a 7-point categorical rating; scores range from 1, indicating "markedly improved," to 4, indicating "

NDC 47781-405-11

Rx only

**RIVASTIGMINE
TRANSDERMAL
SYSTEM**

Delivers 13.3 mg/24 hours

For Transdermal Use Only.

**To avoid possible burns, remove
Rivastigmine Transdermal
System before undergoing an MRI
(magnetic resonance imaging) procedure.**

Contains: 1 System



Made in Germany
Dist. by: Alvogen, Inc.
Pine Brook, NJ 07058 USA

405-11-00 Rev. 09/2014

 Alvogen®

To open, use scissors to cut along dotted line.

See package insert for complete application instructions. **Wear only 1 patch at a time.**

Replace with a new patch every 24 hours.

Do not cut patch.

Apply patch to intact skin immediately after removal from pouch.

Keep out of reach of children.

Retain this pouch for discarding the patch after use.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

LOT

EXP

NDC 47781-305-11

Rx only

**RIVASTIGMINE
TRANSDERMAL
SYSTEM**

Delivers 9.5 mg/24 hours

For Transdermal Use Only.
To avoid possible burns, remove
Rivastigmine Transdermal
System before undergoing an MRI
(magnetic resonance imaging) procedure.

Contains: 1 System

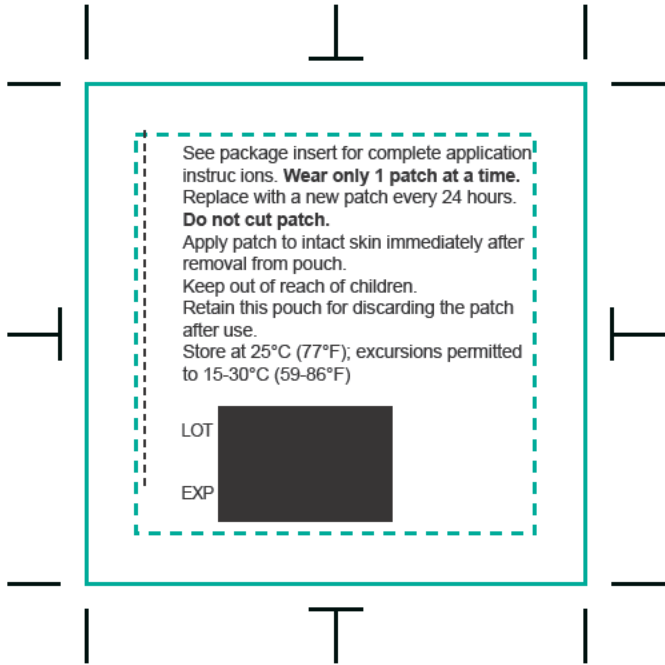


Made in Germany
Dist. by: Alvogen, Inc.
Pine Brook, NJ 07058 USA

305-11-00 Rev. 09/2014

Alvogen®

To open, use scissors to cut along dotted line.



NDC 47781-304-11 Rx only

**RIVASTIGMINE
TRANSDERMAL
SYSTEM**

Delivers 4.6 mg/24 hours

For Transdermal Use Only.
To avoid possible burns, remove
Rivastigmine Transdermal
System before undergoing an MRI
(magnetic resonance imaging) procedure.

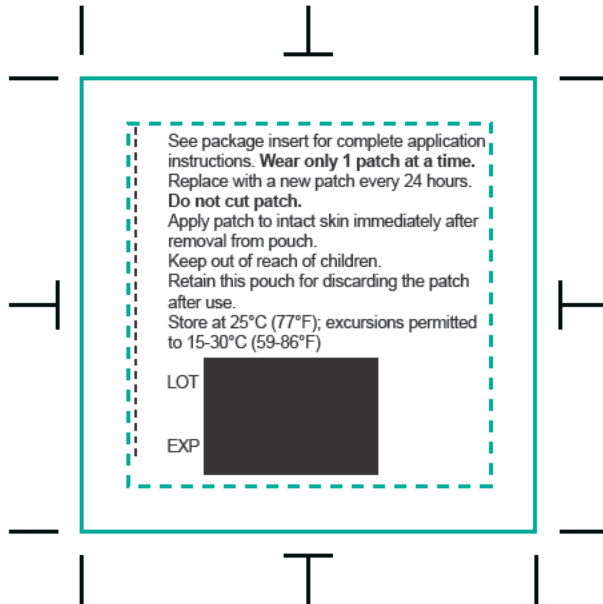
Contains: 1 System

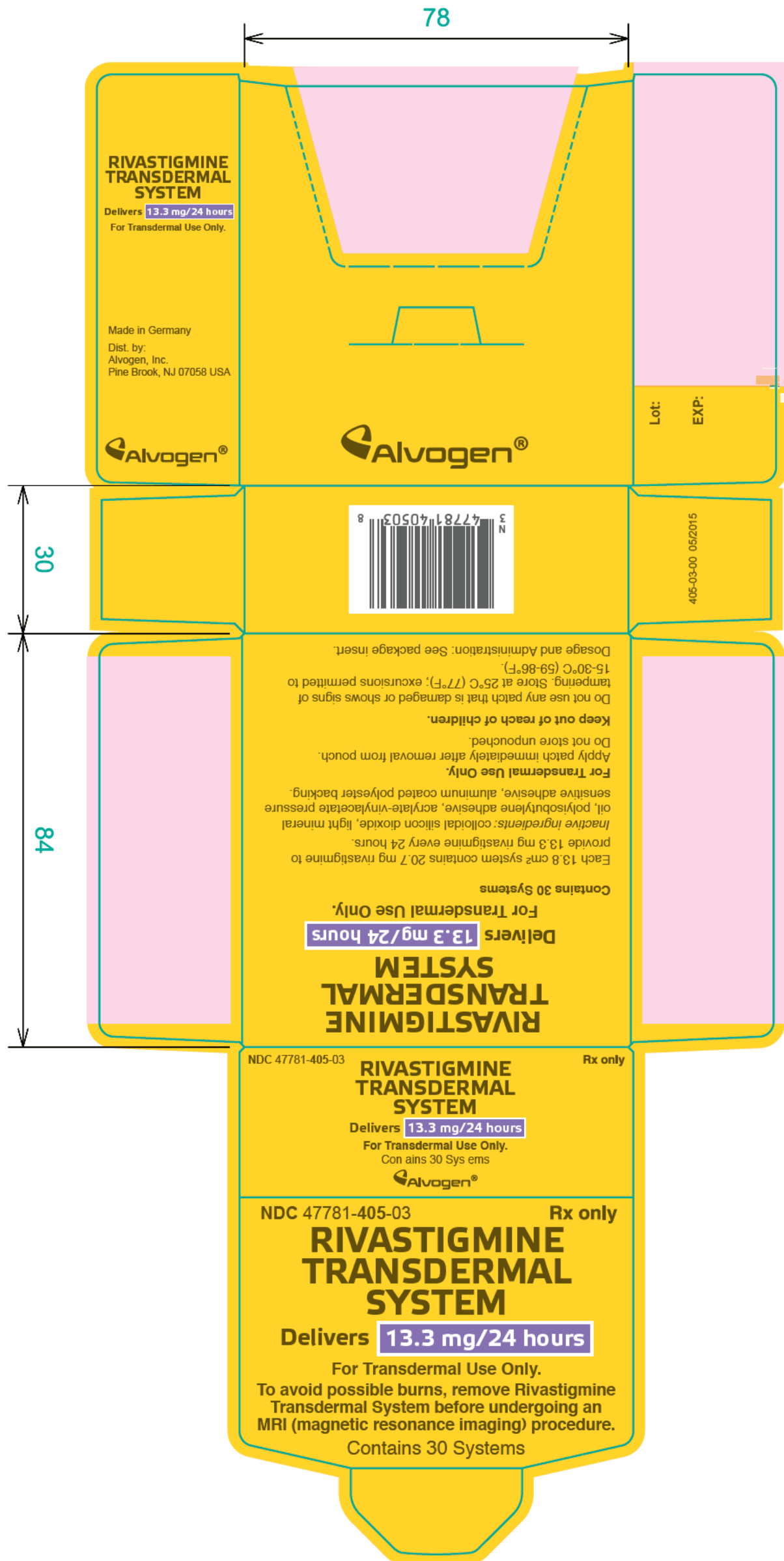


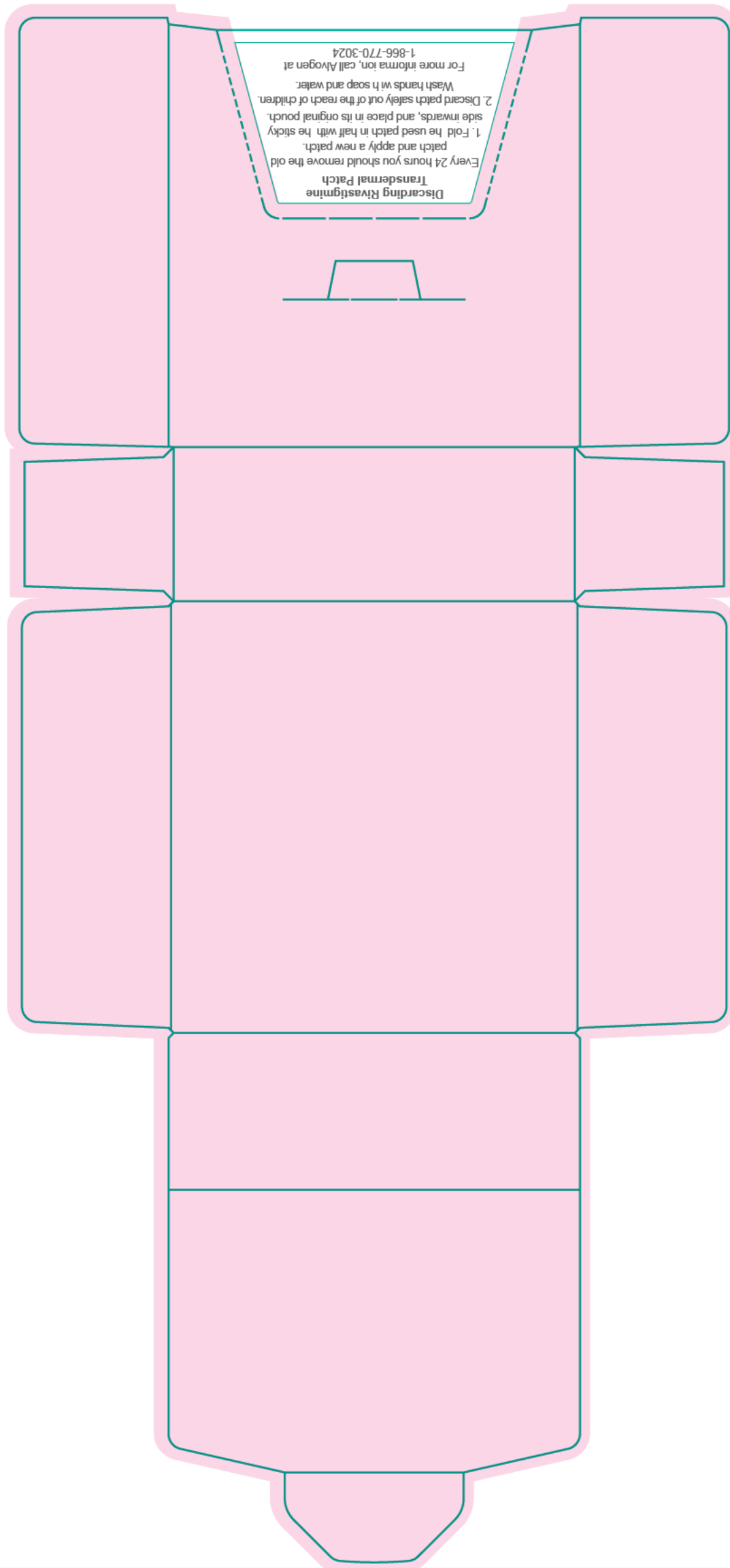
Made in Germany
Dist. by: Alvogen, Inc.
Pine Brook, NJ 07058 USA

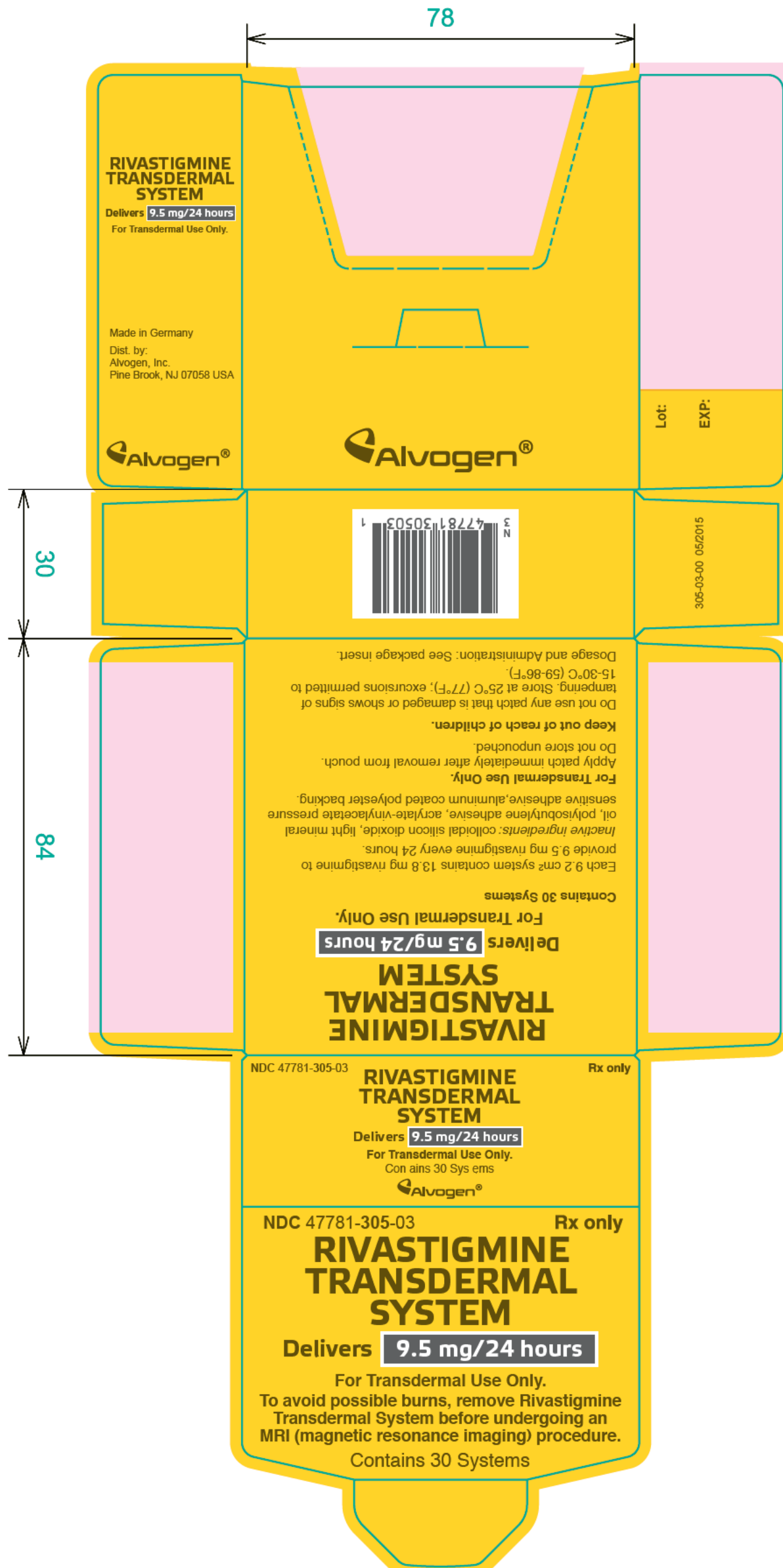
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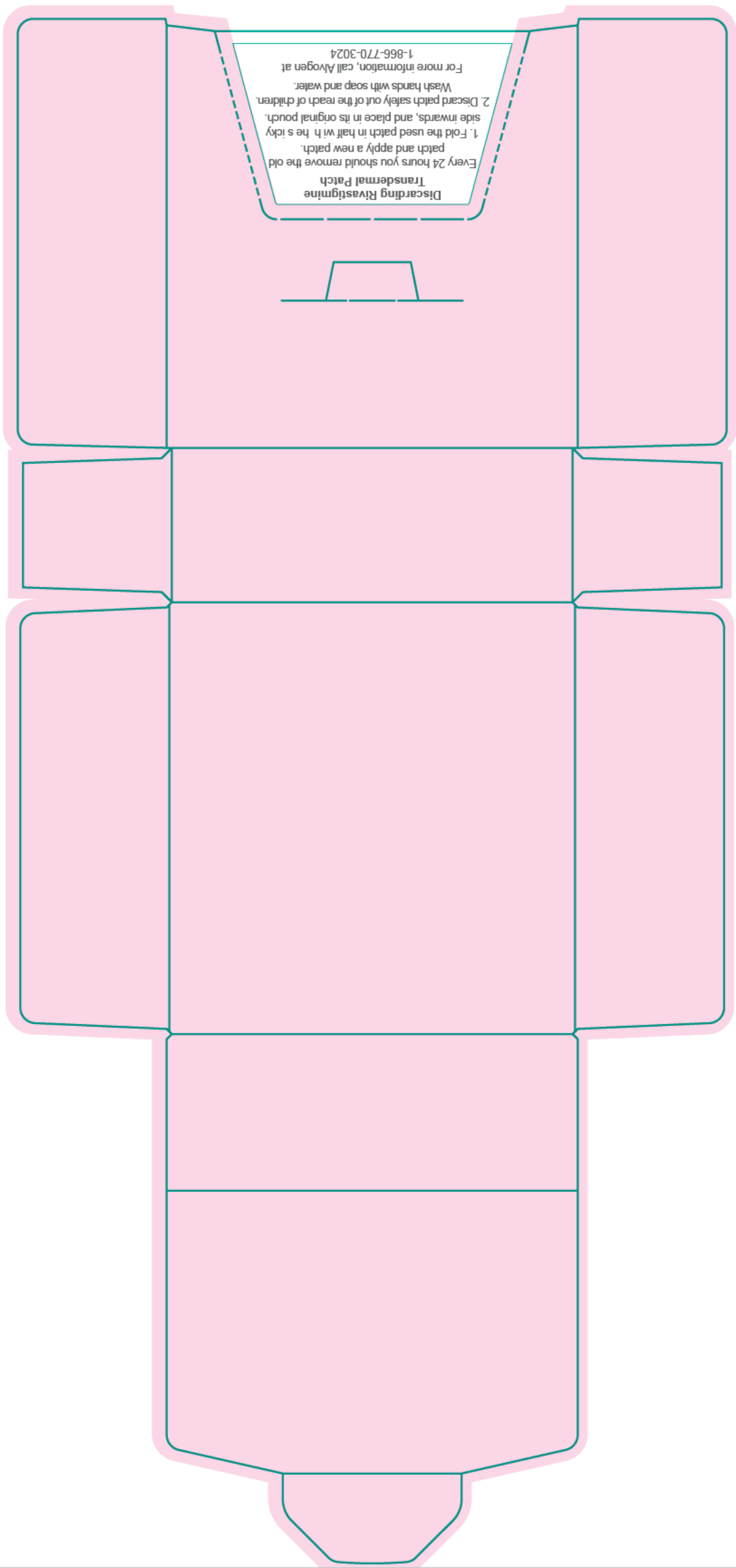
304-11-00 Rev. 09/2014 

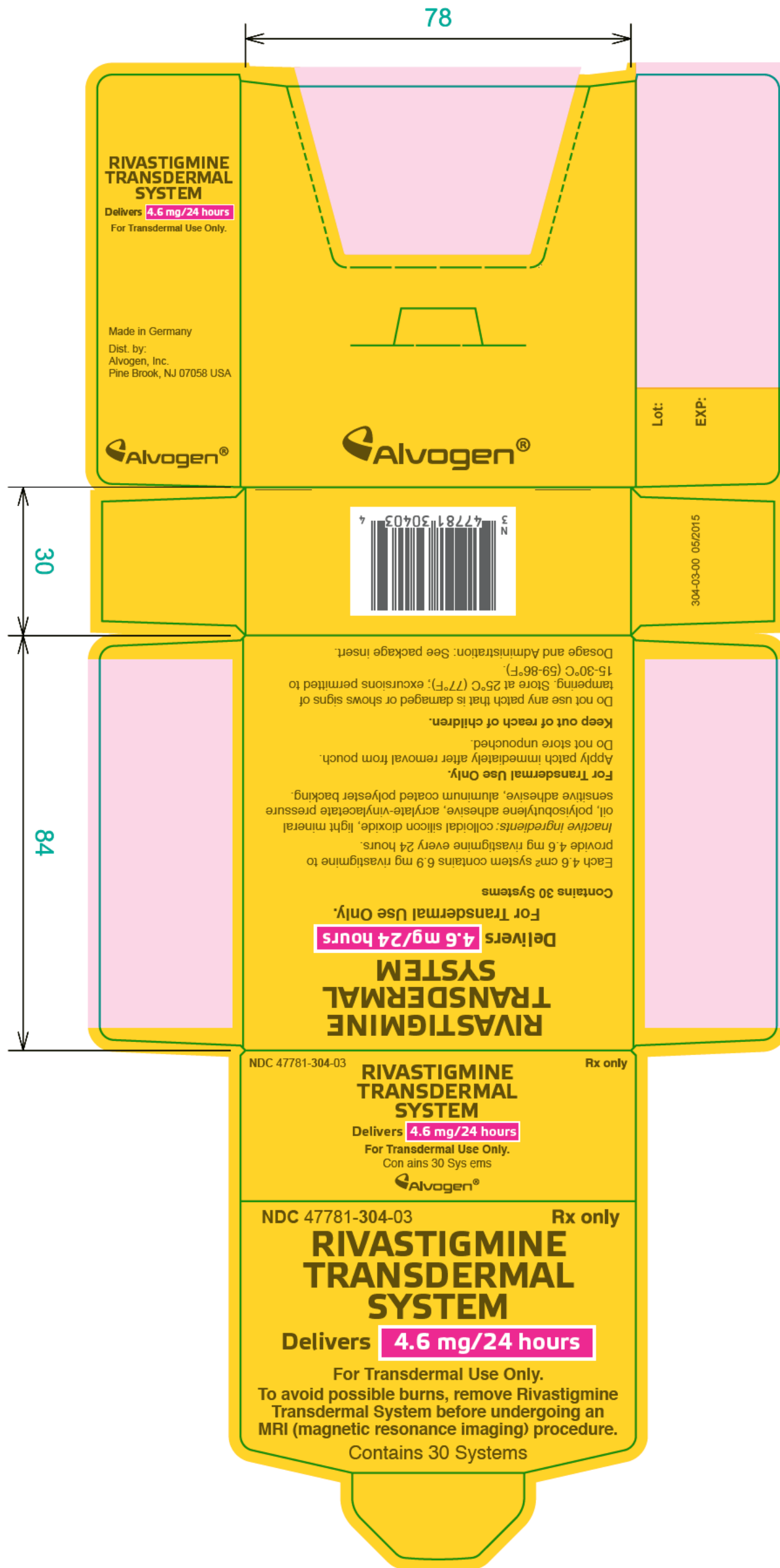




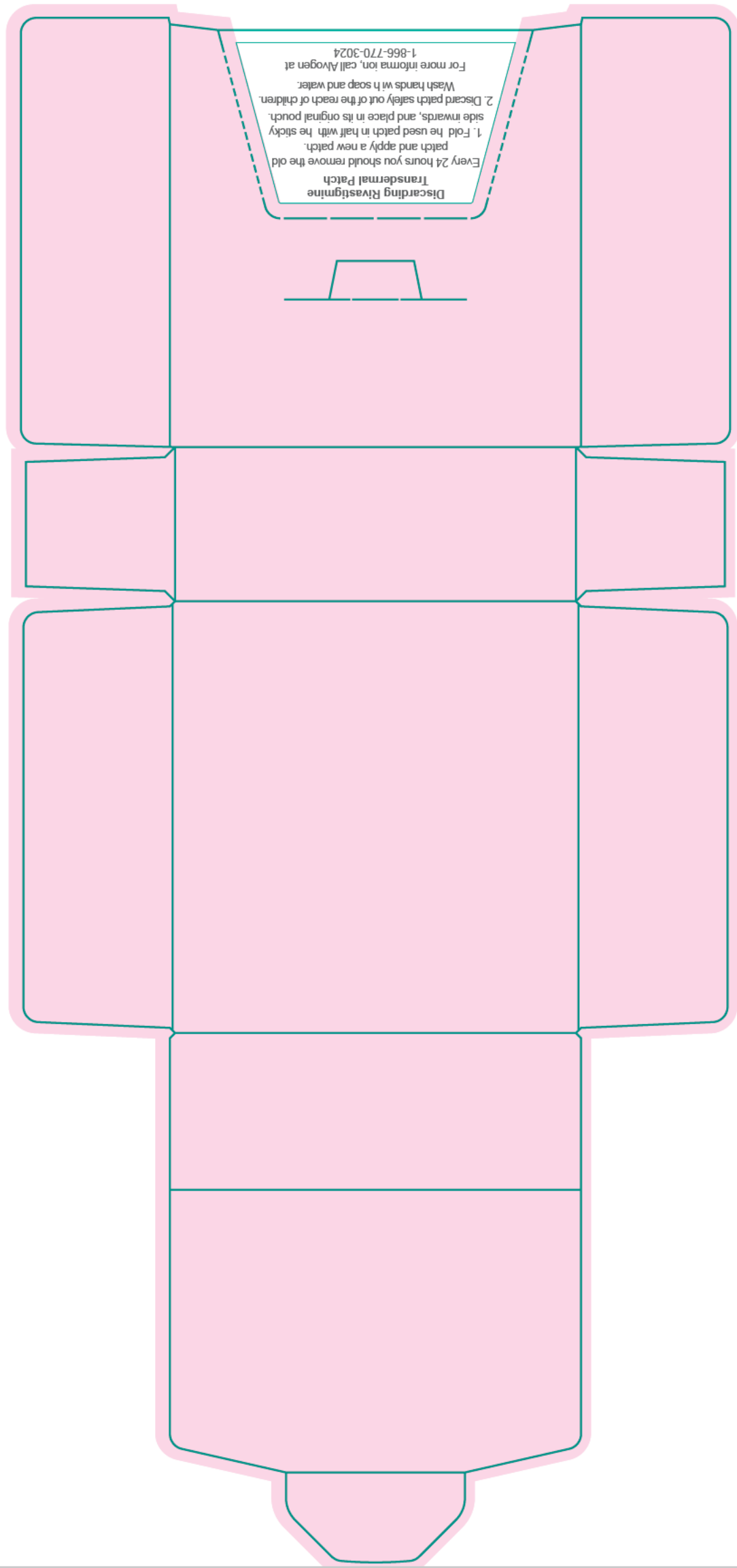








(b) (4)



Discarding Rivastigmine
Transdermal Patch

Every 24 hours you should remove the old
patch and apply a new patch.

1. Fold the used patch in half with the sticky
side inwards, and place in its original pouch.

2. Discard patch safely out of the reach of children.

Wash hands with soap and water.

For more information, call Alvogen at
1-866-770-3024



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 204403

LABELING REVIEWS

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	6/18/2015
ANDA Number(s)	204403
Review Number	3
Applicant Name	Alvogen Inc.
Established Name & Strength(s)	Rivastigmine Transdermal System
Proposed Proprietary Name	None
Submission Received Date	5/14/2015 and 6/16/2015
Labeling Reviewer	Jim Barlow
Labeling Team Leader	Sarah Park
Review Conclusion ☐ ACCEPTABLE – No Comments. ☒ ACCEPTABLE – Include Post Approval Comments ☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant. *Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.	

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

N/A

1.2 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.

These comments will be addressed post approval (in the first labeling supplement review).

Yes

PACKAGE INSERT – Revise the Highlights Limitation Statement as follows:

These highlights do not include all the information needed to use RIVASTIGMINE TRANSDERMAL SYSTEM safely and effectively. See full prescribing information for RIVASTIGMINE TRANSDERMAL SYSTEM.

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment. Include the previous review(s) finalized date(s). 04/27/2015.

APPEARS THIS WAY ON
ORIGINAL

Reviewer Comments: The firm responded to the deficiencies listed below under GENERAL COMMENTS -

1. GENERAL COMMENTS

You submitted proposed labeling that omits the 13.3 mg/24 hour strength for treatment of mild to moderate dementia of the Alzheimer's Type (AD) as well as for the treatment of mild to moderate dementia associated with Parkinson's Disease (PDD) approved in supplement #16 under NDA 022083.

The Agency has determined that it will not permit ANDA applicants to "carve-out" from the labeling the 13.3 mg/24 hour strength for treatment of the already approved indications mild to moderate AD and PDD. Even though the NS exclusivity is solely associated with the 13.3 mg/24 hour strength, the exclusivity effectively blocks the approval of the 4.6 mg/24 hour and 9.5 mg/24 hour strengths until August 31, 2015.

FDA has determined that omission of language associated with this new strength will render your proposed drug product less effective than the RLD for the proposed remaining, non-protected conditions of use, not affording the patient the same therapeutic effect. Such differences in labeling between your proposed product and the RLD are not permissible under 21 CFR 314.127(a)(7).

Thus the Agency cannot accept your proposal to omit from your labeling the 13.3 mg/24 hour strength for treatment of mild to moderate dementia of the Alzheimer's Type as well as the treatment of mild to moderate dementia associated with Parkinson's Disease based on 21 CFR 314.94(a)(8)(iv) .

If you are seeking approval after the expiration of the NS exclusivity on August 31, 2015, please address the [REDACTED] (b) (4) [REDACTED] (b) (4) .

2. CARTON

Please revise to include discarding instructions attached to the carton to be in accord with the RLD.

3. PRESCRIBING INFORMATION

- a. Revise HIGHLIGHTS OF PRESCRIBING INFORMATION to read as follows –

RIVASTIGMINE transdermal system
Initial US Approval: 2000

- b. Please revise to include the 13.3 mg/24 hr strength back in to the How Supplied section.

Also see below information based on a meeting between the firm, the Chemistry Division and the Labeling Division held on 6/12/2015: (Acceptable)

- a) “Cover Sheet”: The cover sheet can also be referred to as a (b) (4) and its purpose is to prevent the transdermal system from sticking to the inside of the pouch. The firm’s patient instructions should include a (b) (4) step following Step 2: Remove the Rivastigmine Patch from the pouch. However, this instruction is missing from the text and the figures, which might cause confusion for the patients. Thus, our concern is that the “Cover Sheet” is shown in Figure A, but the patient is not instructed what to do with it.
- b) “Protective Liners”: In order to avoid confusion, the firm’s terminology should be consistent. However, in Step 3, the firm repeatedly changes terminology from “protective liner” (as shown in Figure A) to “adhesive liner” then “protective liner” then (b) (4) (b) (4). Thus, the firm uses four different terms for the same component of the system. In addition, the use of “protective liner” is particularly confusing because it combines terms used to define two different components in Figure A.

Response: Alvogen discussed and the Agency acknowledged during the telephone conference that the text used in its Patient Information Sheet mirrors that of the RLD. Alvogen also acknowledges that a statement to appropriately instruct patients to (b) (4) Information Sheet and that the term (b) (4) is best replaced by the term “Protective Liner”. As such, Alvogen agrees to amend the Patient Information Sheet at Step 4 to read: “Apply the sticky (adhesive) side of the Rivastigmine Patch onto your chosen area of skin and then peel off the other side of the protective liner as well as the cover sheet and discard both” and to replace the term (b) (4) with “Protective Liner” throughout the Patient Information Sheet.

Although Alvogen had initially suggested that this change be considered “post – approval” by the Agency, it is willing to initiate the change prior to approval. We have revised the labeling accordingly. Please refer

to Module 1.14.2.2 for the revised package insert (**word** and **pdf** versions), provided in final print format and SPL provided in **Module 1.14.2.3**. Side-by-side comparisons of the current proposed labeling with the previously submitted labeling is provided in **Module 1.14.3.1**.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: None

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s).

Reviewer Comments:

Intra-agency meeting between CMC and Labeling regarding aluminum backing:

The Division of Chemistry noted an issue in their review dated 10/2/2014 regarding aluminum backing being utilized for their proposed patch. However, based on an intra-agency meeting between CMC and Labeling, it was decided that, even though the RLD does not have aluminum backing, this ANDA’s proposal to have aluminum backing and to add the warning statements is acceptable. In addition, it was found that hospital policy requires every patient to remove all transdermal systems prior to an MRI

procedure.



6/12/15 meeting between Industry, CMC and Labeling:

- a. CMC noted that this ANDA proposed a Cover Sheet in the pouch to assist in the easy removal of the transdermal system from the pouch do to leakage of the product (which is considered normal).
(b) (4)
- b. Also the (b) (4) was changed to “Protective Liner” to avoid confusion with the term “Cover Sheet”.
- c. **POST APPROVAL** – A commitment was made by the firm to revise the IMPRINT from (b) (4) to “RIVASTIGMINE” to be in accord with the Division of Chemistry requirements.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR’s Repository files? YES

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on OGD’s SharePoint? NO

If Yes, please explain.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling
(Check the box used as the Model Labeling)

MOST RECENTLY APPROVED NDA MODEL LABELING N022083

NDA#/Supplement# (S-000 if original): S-020

Supplement Approval Date: 02/03/2015

Proprietary Name: Exelon©

Established Name: Rivastigmine Transdermal System

Description of Supplement:

This "Prior Approval" supplemental new drug application provides revisions to the labeling for Exelon Transdermal Patch. Included are proposed revisions throughout the prescribing information.

MOST RECENTLY APPROVED ANDA MODEL LABELING N/A

ANDA#/Supplement# (S-000 if original):

Supplement Approval Date:

Proprietary Name:

Established Name:

Description of Supplement:

TEMPLATE (e.g., BPCA, PREA, Carve-out):

OTHER (Describe):

Carve-out proposed for protected information (13.3 mg/24 hr patch) (It has been decided by the Agency that the 13.3 mg patch and its' associated information must stay in the labeling due to the efficacy of the drug product. **(We refer you to the Division of Labeling Review repository for guidance)**

Please note that the firms proposed carve out of the NPP exclusivity [(13.3 mg/24 hours nominal release rate, (b) (4)

(b) (4)

(b) (4)

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **NO**

Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

See **DEFICIENCY COMMENT** above [section 2 (Previous Labeling Review, Deficiencies, Firm's Response, and Reviewer's Assessment)] regarding the chemistry deficiency brought to the attention of labeling.

3.3 MODEL CONTAINER LABELS

Model labels and carton labeling. (Annual report submitted 8/28/2014)



See package insert for complete application instructions. **Wear only 1 patch at a time.** Replace with a new patch every 24 hours. **Do not cut patch.** Apply patch to intact skin immediately after removal from pouch. Change the location of each new patch. Keep out of the reach of children. Retain this pouch for discarding the patch after use. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Mfd. by: LTS Lohmann Therapy Systems Corp.
West Caldwell, New Jersey 07006
Dist. by: Novartis Pharmaceuticals Corp.
East Hanover, New Jersey 07936



©Novartis

5003655

NDC 0078-0502-61

Rx only



EXELON[®] PATCH

(rivastigmine transdermal system)

Delivers **9.5 mg/24 hours**

For Transdermal Use Only.

Contains 1 System



N(01)00300780502610

EXP

LOT

5003655

NOVARTIS

To open, use scissors to cut along dotted line.

Discarding EXELON PATCH

Every 24 hours you should remove the old patch and apply a new patch.

1. Fold the used patch in half with the sticky side inwards, and place in its original pouch.
2. Discard patch safely out of the reach of children. Wash hands with soap and water.

For more information, visit
www.EXELONPATCH.com
or call 1-888-76-PATCH (1-888-767-2824).



EXELON[®] PATCH

(rivastigmine transdermal system)

Contains 30 Systems

Each 10 cm² system contains 18 mg rivastigmine to provide 9.5 mg rivastigmine every 24 hours.

Inactive components: acrylic copolymer; poly(butylmethacrylate, methylmethacrylate); silicone adhesive applied to a flexible polymer backing film; silicone oil; vitamin E.

For Transdermal Use Only
Apply patch immediately after removal from pouch.
Do not store unpouched.

Keep out of the reach of children.

Do not use any patch that is damaged or shows signs of tampering.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Dosage and Administration: See package insert.

www.EXELONPATCH.com ©Novartis 5003658

Product of Switzerland



EXELON[®] PATCH

(rivastigmine transdermal system)

Manufactured by:
LTS Lohmann Therapy Systems Corporation
West Caldwell, New Jersey 07006

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936



NDC 0078-0502-15

Rx only

EXELON[®] PATCH

(rivastigmine transdermal system)

Each System Delivers **9.5 mg/24 hours**

For Transdermal Use Only

Contains 30 Systems



3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	6/7/2015	No	N/A	N/A
PF	6/7/2015	No, however it is currently listed as In-Process Revision	proposed	(b) (4)

Reviewer Comments:

None

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on [Click here to enter a date.](#)

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
6316023	1/8/2019			Paragraph IV	6/12/2012	No Impact; Litigation resulted in favor of the defendant on 3/16/2015 submission
6335031	1/8/2019			Paragraph IV	6/12/2012	No Impact; Litigation resulted in favor of the defendant on 3/16/2015 submission

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

None

Table 4 provides Orange Book exclusivities for the Model Labeling and

ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
NS	Aug 31, 2015	New Strength	See below COMMENTS	5/14/2015 via cover letter to be in accord with the Agencies request.	Included after the Agencies decision. No impact
NPP	June 27, 2016	New Patient Population	See below COMMENTS	10/2/2014	Carved Out

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **YES**

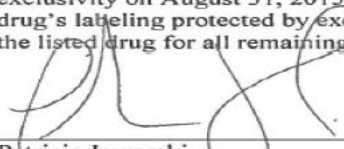
Reviewer Comments:

1.3.5.3 EXCLUSIVITY STATEMENT

According to information published in the "Approved Drug Products with Therapeutic Equivalence Evaluations" for Exelon® Patch (Rivastigmine Transdermal System), there are two exclusivities listed for the 13.3 mg strength as listed below. Alvogen certified in the Additional Strength Amendment dated January 22, 2013 that it would not market the 13.3 mg/24 hr strength until expiry of the New Strength (NS) exclusivity on August 31, 2015.

Exclusivity	Expires
1. New Strength (NS)	August 31, 2015
2. New Patient Population (NPP)	June 27, 2016

Pursuant to 21 C.F.R. § 314.94(a)(8)(iv), Alvogen has removed text associated with the NPP exclusivity from its label and intends to market the 13.3 mg/24 hr strength upon the later of: i) expiry of the NS exclusivity on August 31, 2015 and ii) approval of its 13.3 mg/hr strength. The aspects of the listed drug's labeling protected by exclusivity, do not render Alvogen's drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use, as per, 21 C.F.R. §314.127(a)(7).


 Patricia Jaworski
 Vice President, Regulatory Affairs

10-2-14
 Date

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the DESCRIPTION section, HOW SUPPLIED section and manufacturing statements of the Prescribing Information when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section? **NO**
 Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED? **YES**
 Are there changes to the manufacturing statements? **NO**
 If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section

Table 5: Comparison of DESCRIPTION Section

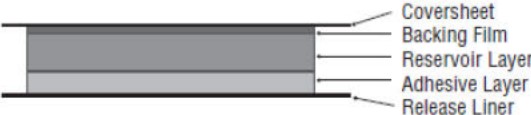
Previous Labeling Review	Currently Proposed	Assessment
The patch comprises a multi-layer laminate containing the coversheet, backing layer, reservoir layer, adhesive layer, and release liner as described below. The release liner is removed and discarded prior to use. See Figure 1: Figure 1: Schematic drawing of Rivastigmine Transdermal System  • a cover sheet: siliconised polyethylene terephthalate film • a backing liner: Polyethylene /thermoplastic resin / aluminum coated polyester film • an active reservoir layer containing the active pharmaceutical ingredient • an adhesive matrix layer • a release liner: fluoropolymer coated polyester film Excipients within the formulation include colloidal silicon dioxide, light mineral oil, polyisobutylene adhesive, acrylate-vinylacetate pressure, sensitive adhesive, aluminum coated polyester backing.	Rivastigmine Patch is for transdermal administration. The patch comprises a multi-layer laminate containing the coversheet, backing film, reservoir layer, adhesive layer, and release liner as described below. The release liner is removed and discarded prior to use. See Figure 1 for a detailed illustration. • a cover sheet: siliconised polyethylene terephthalate film • a backing film: Polyethylene / thermoplastic resin / aluminum coated polyester film • an active reservoir layer containing the active pharmaceutical ingredient • an adhesive matrix layer • a release liner: fluoropolymer coated polyester film Figure 1: Schematic drawing of Rivastigmine Transdermal System  Coversheet Backing Film Reservoir Layer Adhesive Layer Release liner Excipients within the formulation include colloidal silicon dioxide, light mineral oil, polyisobutylene adhesive, acrylate-vinylacetate pressure sensitive adhesive, aluminum coated polyester backing.	No changes.

Table 6: Comparison of HOW SUPPLIED Section		
Previously Labeling Review	Currently Proposed	Assessment

APPEARS THIS WAY ON ORIGINAL

Table 6: Comparison of HOW SUPPLIED Section

Rivastigmine Patch 4.6 mg/24 hours Each patch of 4.6 cm² contains 6.9 mg rivastigmine with <i>in-vivo</i> release rate of 4.6 mg/24 hours. Carton of 30.....NDC (b) (4)	<u>Rivastigmine Patch: 4.6 mg/24 hours</u> Each patch of 4.6 cm² contains 6.9 mg rivastigmine with <i>in vivo</i> release rate of 4.6 mg/24 hours. Carton of 30.....NDC 47781-304-03	
Rivastigmine Patch 9.5 mg/24 hours Each patch of 9.2 cm² contains 13.8 mg rivastigmine with <i>in-vivo</i> release rate of 9.5 mg/24 hours. Carton of 30.....NDC (b) (4)	<u>Rivastigmine Patch: 9.5 mg/24 hours</u> Each patch of 9.2 cm² contains 13.8 mg rivastigmine with <i>in vivo</i> release rate of 9.5 mg/24 hours. Carton of 30.....NDC 47781-305-03	Firm has added in the 13.3 mg/24 hr patch per Agencies request. Acceptable
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep Rivastigmine Patch (rivastigmine transdermal system) in the individual sealed pouch until use. Used systems should be folded, with the adhesive surfaces pressed together, and discarded safely. Each pouch contains one patch.	<u>Rivastigmine Patch: 13.3 mg/24 hours</u> Each patch of 13.8 cm² contains 20.7 mg rivastigmine with <i>in vivo</i> release rate of 13.3 mg/24 hours. Carton of 30.....NDC 47781-405-03 Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Keep Rivastigmine Patch in the individual sealed pouch until use. Each pouch contains 1 patch. Used systems should be folded, with the adhesive surfaces pressed together, and discarded safely.	

Table 7: Manufactured by statement		
Previously Labeling Review	Currently Proposed	Assessment
Made in Germany Distributed by: Alvogen, Inc. Pine Brook, NJ 07058 USA	Made in Germany Distributed by: Alvogen, Inc. Pine Brook, NJ 07058 USA	No changes. Acceptable

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:

See information above under section 2 and section 2.2 listed above.

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments:

- a. See information above under section 2 and section 2.2 above.
- b. Please note that OGD Policy assisted in preparing a statement to be sent to the firms based on the fact that they believed that carving out the 13.3 mg/24 hr patch protected by a NS (new Strength) exclusivity would render this drug product less efficacious and therefore, would be impermissible.

GENERAL COMMENTS

You submitted proposed labeling that omits the 13.3 mg/24 hour strength for treatment of mild to moderate dementia of the Alzheimer's Type (AD) as well as for the treatment of mild to moderate dementia associated with Parkinson's Disease (PDD) approved in supplement #16 under NDA 022083.

The Agency has determined that it will not permit ANDA applicants to "carve-out" from the labeling the 13.3 mg/24 hour strength for treatment of the already approved indications mild to moderate AD and PDD. Even though the NS exclusivity is solely associated with the 13.3 mg/24 hour strength, the exclusivity effectively blocks the approval of the 4.6 mg/24 hour and 9.5 mg/24 hour strengths until August 31, 2015.

FDA has determined that omission of language associated with this new strength will render your proposed drug product less effective than the RLD for the proposed remaining, non-protected conditions of use, not affording the patient the same therapeutic effect. Such differences in labeling between your proposed product and the RLD are not permissible under 21 CFR 314.127(a)(7).

Thus the Agency cannot accept your proposal to omit from your labeling the 13.3 mg/24 hour strength for treatment of mild to moderate dementia of the Alzheimer's Type as well as the treatment of mild to moderate dementia associated with Parkinson's Disease based on 21 CFR 314.94(a)(8)(iv)] .

If you are seeking approval after the expiration of the NS exclusivity on August 31, 2015, please address the

(b) (4)

(b) (4)

- c. Please note that a consult was sent to Division of Neurology Drug Products (DNP) for seeking concurrence with Policy's decision. A response was received by DLR on 7/17/2015.

OND's response received 7/17/2015 states the following:

As is described in the product label for the Exelon Patch, the superiority of the 13.3mg/24h patch dose over the 9.5mg/24h dose was demonstrated in a 48-week efficacy trial. A detailed description of the results of that study is beyond the scope of this memo. It must also be noted, though, that while the 13.3mg/24h dose was statistically superior to the 9.5mg/24h dose in that trial, the magnitude of any increased benefit was very modest (as is the case with all approved AD therapies). There is evidence to support the position that the omission of the 13.3mg/24h dose from a generic product label would lead to use of a dose (9.5mg/24h) that is less effective

than the omitted dose (13.3mg/24h).

(b) (4)

(b) (4)

(b) (4)

DLR will proceed with retaining the 13.3 mg/24 hour strength as previously decided by OGD Policy.

Please note that OND did not share any comments related to the NPP (New Patient Population) exclusivity proposed carve-outs. This exclusivity expires on 6/27/2016. Since no comments were made, it can be assumed that these carve-outs are acceptable.

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for each material analyzed in this review.

If this review is acceptable, then all pertinent labeling pieces must be entered for both tables.

For each row, if you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Date	Recommendation
Container (pouch)	Final	1s (4.6 mg/24 hr.; 9.5 mg/24 hr. & 13.3 mg/24 hr.)	10/2/2014	Acceptable
Blister	N/A			
Unit Dose Cartons	Final	30s (4.5 mg/24 hr.; 9.5 mg/24 hr. & 13.3 mg/24 hr.)	5/14/2015	Acceptable
(Other – specify)	N/A			
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	Revision Date and/or Code	Submission Date	Recommendation
Prescribing Information	Final	06/2015	6/16/2015	Acceptable
Medication Guide	N/A			
Patient Information/Instructions for Use	Final	06/2015	6/16/2015	Acceptable
SPL Data Elements		06/2015	6/16/2015	Data elements are acceptable

* Post-approval revision

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

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review 4/24/15

ANDA Number 204403

Review Cycle Number Cycle #2

Applicant Name Alvogen Inc.

Established Name Rivastigmine Transdermal System

Strength(s) 4.6 mg/24 hr., 9.5 mg/24 hr. and 13.3 mg/24 hr.

Proposed Proprietary Name None

DARRTS Received Date 10/2/14 and 2/18/15

Labeling Reviewer Jim Barlow

Labeling Team Leader Lisa Kwok

Review Conclusion

No Comments – The Labels and Labeling are ready for Choose an item.

Minor Deficiency* - Refer to Labeling Deficiencies and Comments for the Letter to Applicant

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

1. GENERAL COMMENTS

You submitted proposed labeling that omits the 13.3 mg/24 hour strength for treatment of mild to moderate dementia of the Alzheimer's Type (AD) as well as for the treatment of mild to moderate dementia associated with Parkinson's Disease (PDD) approved in supplement #16 under NDA 022083.

The Agency has determined that it will not permit ANDA applicants to “carve-out” from the labeling the 13.3 mg/24 hour strength for treatment of the already approved indications mild to moderate AD and PDD. Even though the NS exclusivity is solely associated with the 13.3 mg/24 hour strength, the exclusivity effectively blocks the approval of the 4.6 mg/24 hour and 9.5 mg/24 hour strengths until August 31, 2015.

FDA has determined that omission of language associated with this new strength will render your proposed drug product less effective than the RLD for the proposed remaining, non-protected conditions of use, not affording the patient the same therapeutic effect. Such differences in labeling between your proposed product and the RLD are not permissible under 21 CFR 314.127(a)(7).

Thus the Agency cannot accept your proposal to omit from your labeling the 13.3 mg/24 hour strength for treatment of mild to moderate dementia of the Alzheimer’s Type as well as the treatment of mild to moderate dementia associated with Parkinson’s Disease based on 21 CFR 314.94(a)(8)(iv)] .

If you are seeking approval after the expiration of the NS exclusivity on August 31, 2015, please address the

(b) (4)

2. CARTON

Please revise to include discarding instructions attached to the carton to be in accord with the RLD.

3. PRESCRIBING INFORMATION

- a. Revise HIGHLIGHTS OF PRESCRIBING INFORMATION to read as follows –

RIVASTIGMINE transdermal system
Initial US Approval: 2000

- b. Please revise to include the 13.3 mg/24 hr strength back in to the How Supplied section.

Submit your revised labeling electronically in SPL and in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drugs labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

- 1.1 PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, and reviewer's assessment**
In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment. There was only one previous deficiency labeling review finalized on 9/24/13 in DARRTs.

Carton -

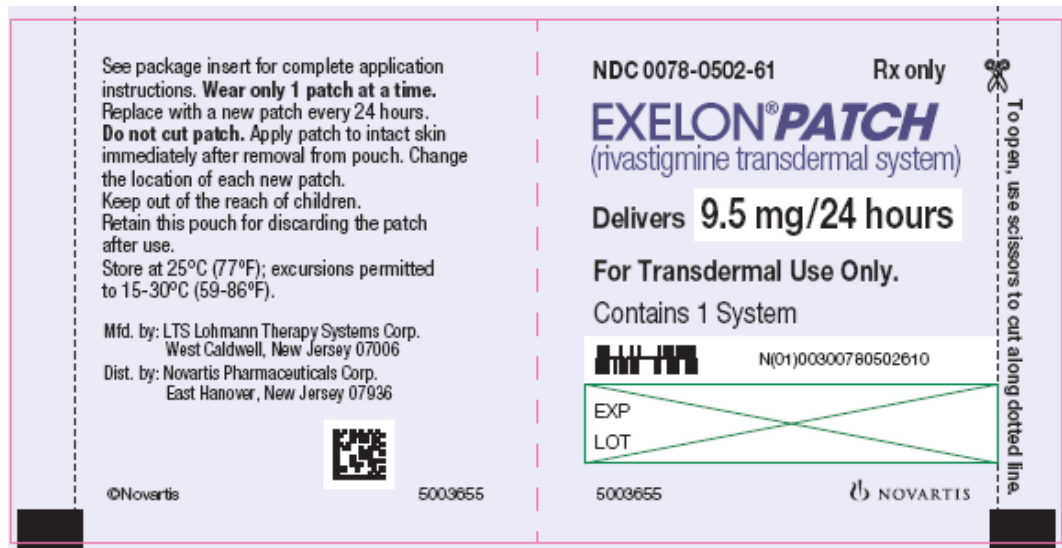
Front panel: Please utilize this sample of the RLD carton as guidance for the layout of your proposed labels. (Note the following recommendations pertain to both proposed strengths).



- a. Place the NDC # and Rx only statement at the top left and right of the label
- b.  (b) (4)
- c. Include the statement "For Transdermal Use Only" on the front panel as well as the side panel to be in accord with the RLD.

2. Individual Pouch -

Please utilize this sample of the RLD pouch as guidance for the layout of your proposed labels. (Note the following recommendations pertain to both proposed strengths).



- a. See comment 1(c.) above
- b. We note that you did not submit a pouch that included instructions and product information on the back side for the 4.6 mg/24 hr and the 9.5 mg/24 hr strength patches. Please revise and submit to be in accord with the reference listed drug.

3. Package Insert and Patient Information Leaflet

We note that revised package insert labeling has been recently approved for the reference listed drug, Exelon® Patch by Novartis (NDA 022083/S-019; approved June 27, 2013) and these revisions are protected by exclusivity. Please address how you will certify regarding this recent update.

Reviewer Comments: *The firm has responded favorably to our deficiency comments from the previous review. They have also updated their labeling to be in accord with the most recently approved labeling for the reference listed drug, Exelon® Patch by Novartis (NDA 022083/S-020; approved February 3, 2015). However, it has been decided by the Agency that the 13.3 mg strength patch CANNOT be carved out of the labeling due to efficacy issues. See deficiency "General Comments" above.*

1.2 ADDITIONAL BACKGROUND INFORMATION THAT IS PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence (s) and/or information date (s).

Reviewer Comments: CMC review of the 10/2/14 amendment is currently in "Progress". However, based on an intra-agency meeting between CMC and Labeling, it was decided that, even though the RLD does not have aluminum backing, this ANDA's proposal to have aluminum backing and to add the warning statements is acceptable. In addition, it was found that hospital policy requires every patient to remove all transdermal systems prior to an MRI procedure.

NDC 47781-304-11 Rx only

RIVASTIGMINE TRANSDERMAL SYSTEM

Delivers 4.6 mg/24 hours
For Transdermal Use Only.
To avoid possible burns, remove
Rivastigmine Transdermal
System before undergoing an MRI
(magnetic resonance imaging) procedure.

Contains: 1 System



Made in Germany
Dist. by: Alvogen, Inc.
Pine Brook, NJ 07058 USA

304-11-00 Rev. 09/2014 

To open, use scissors to cut along dotted line.



2. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Table 1: Review Summary of Container Label and Carton Labeling			
	Packaging Sizes	Submission Date	Recommendation
Container ☐ Draft ☒ FPL	1s (4.6 mg/24 hr.; 9.5 mg/24 hr. & 13.3 mg/24 hr.)	10/2/14	☒ Satisfactory ☐ Revise
Blister ☐ Draft ☐ FPL	N/A		☐ Satisfactory ☐ Revise
Carton ☐ Draft ☐ FPL	N/A		☐ Satisfactory ☐ Revise
Unit Dose Carton ☐ Draft ☒ FPL	30s (4.5 mg/24 hr.; 9.5 mg/24 hr. & 13.3 mg/24 hr.)	10/2/14	☐ Satisfactory ☒ Revise
Table 2 Review Summary of Prescribing Information and Patient Labeling			
	Revision Date and/or code	Submission Date	Recommendation
Prescribing Info ☐ Draft ☒ FPL	2/15	2/18/15	☐ Satisfactory ☒ Revise
Medication Guide ☐ Draft ☐ FPL			☐ Satisfactory ☐ Revise
Patient Information ☐ Draft ☒ FPL	2/15	2/18/15	☐ Satisfactory ☒ Revise
PPI ☐ Draft ☐ FPL			☐ Satisfactory ☐ Revise

3. MODEL CONTAINER LABELS FOR ANDA

In Table 2 below, check all sources for Model container labels and carton labeling (secondary packaging) that applies.

Table 2: Review Model Labeling for Container Label and Carton Labeling (Check all sources that apply)	
Source	Date of source document (i.e. supplement approval date, annual report date)
☐ drugs@fda	
☐ DARRTS	
☒ DailyMed	July 2013
☒ Annual Report	8/28/14
☐ Other	

Model labels and carton labeling. [Insert or paste images below]





4. PRESCRIBING INFORMATION MODEL LABELING

The review model labels and labeling used for comparison to the submitted ANDA labeling are described in Table 3.

Table 3: Review Model Labeling for Prescribing Information and Patient Labeling(Check all that apply)		
☒ MOST RECENTLY APPROVED REFERENCE LISTED DRUG		
NDA: 022083	Proprietary Name: Exelon [®]	Approval date: 2/3/15

Table 3: Review Model Labeling for Prescribing Information and Patient Labeling(Check all that apply)	
S- 020	Description of Supplement: This “Prior Approval” supplemental new drug application provides revisions to the labeling for Exelon Transdermal Patch. Included are proposed revisions throughout the prescribing information.
☐ BPCA or PREA TEMPLATE	
☒ OTHER (Describe): Carve-out proposed for protected information (13.3 mg/24 hr patch) (It has been decided by the Agency that the 13.3 mg patch and its’ associated information must stay in the labeling due to the efficacy of the drug product. See the deficiencies above “General Comments”).	

Reviewer Assessment:

Are the labeling contained in the submission the same as the review model labeling? **NO**
 Are the differences allowed under [21 CFR 314.94\(a\)\(8\)](#)? **No**
 Are the specific requirements for format met under [21 CFR 201.57\(new\)](#) or [201.80\(old\)](#)? **YES**
 Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments: No. the firm is carving out information regarding the addition of the NS. Also the firm has included information regarding MRI and skin burns. Something the RLD does not include in their labeling. (See deficiency comment and additional background information 1.2 above).

5. PATENTS AND EXCLUSIVITIES

Table 4 describes how the applicant certified to the Orange Book patent(s) for the Model Labeling and how this certification impacts the ANDA labels and labeling. For applications that have no patents N/A is entered in the patent number column.

Table 4: Impact of Model Labeling Patents on ANDA Labeling					
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	How Applicant Filed	Labeling Impact
6316023	Jan 8, 2019			Paragraph IV	No Impact
6335031	Jan 8, 2019			Paragraph IV	No Impact

Reviewer Assessment:

Is the applicant’s “patent carve out” acceptable? **NA**

Reviewer Comments: Acceptable

Table 5 describes how the expiration of the Orange Book exclusivities for the Model Labeling impacts the ANDA labels and labeling. For applications that have no exclusivities N/A is entered in the Exclusivity Code column.

Exclusivity Code	Exclusivity Code Definition	Exclusivity Expiration	Labeling Impact
<u>NS</u>	New Strength	Aug 31, 2015	Carved Out. However, the Agency has decided that this information CANNOT be carved out of the labeling because it decreases the efficacy of this drug product. See deficiency comments above.
<u>NPP</u>	New Patient Population	Jun 27, 2016	Carved Out

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NO**

Reviewer Comments:

1.3.5.3 EXCLUSIVITY STATEMENT

According to information published in the "Approved Drug Products with Therapeutic Equivalence Evaluations" for Exelon[®] Patch (Rivastigmine Transdermal System), there are two exclusivities listed for the 13.3 mg strength as listed below. Alvogen certified in the Additional Strength Amendment dated January 22, 2013 that it would not market the 13.3 mg/24 hr strength until expiry of the New Strength (NS) exclusivity on August 31, 2015.

Exclusivity	Expires
1. New Strength (NS)	August 31, 2015
2. New Patient Population (NPP)	June 27, 2016

Pursuant to 21 C.F.R. § 314.94(a)(8)(iv), Alvogen has removed text associated with the NPP exclusivity from its label and intends to market the 13.3 mg/24 hr strength upon the later of: i) expiry of the NS exclusivity on August 31, 2015 and ii) approval of its 13.3 mg/hr strength. The aspects of the listed drug's labeling protected by exclusivity, do not render Alvogen's drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use, as per, 21 C.F.R. §314.127(a)(7).

Patricia Jaworski
Vice President, Regulatory Affairs

10-2-14
Date

6. United States Pharmacopeia (USP) & Pharmacopeia Forum (PF)

We searched the [USP and PF](#) to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph and determined how the monograph impacts the ANDA labeling with respect to packaging and storage. The results of this search are provided in Table 6.

	Date Searched	Monograph? YES or NO	Labeling statements found NA if no monograph
USP	4/25/2015	NO	N/A
PF	4/25/2015	NO	N/A

7. DESCRIPTION and HOW SUPPLIED sections and Manufactured by Statement

Did the Description, and How Supplied Sections and Manufactured by statement change from the previous review? **No**

If YES complete the relevant Tables below, if NO, go to section 8

Tables 8, 9, and 10 describe if any changes have occurred in the DESCRIPTION (e.g., inactives), HOW SUPPLIED (e.g., description of dosage form, package sizes and drug product manufacturing statement), and

manufacturing statements sections of the Prescribing Information when compared to the previous labeling review.

Table 8: Comparison of DESCRIPTION Section		
Previous Labeling Review	Currently Proposed	Assessment
The patch comprises a multi-layer laminate containing the coversheet, backing layer, reservoir layer, adhesive layer, and release liner as described below. The release liner is removed and discarded prior to use. See Figure 1 for a detailed illustration. • a cover sheet: siliconised polyethylene terephthalate film • a backing liner: Polyethylene / thermoplastic resin / aluminium coated polyester film • an active reservoir layer containing the active pharmaceutical ingredient • an adhesive matrix layer • a release liner: fluoropolymer coated polyester film  Figure 1: Schematic drawing of Rivastigmine-TDS Excipients within the formulation include colloidal silicon dioxide, light mineral oil, polyisobutylene adhesive, acrylate-vinylacetate pressure sensitive adhesive, polyester backing.	The patch comprises a multi-layer laminate containing the coversheet, backing (b) (4) reservoir layer, adhesive layer, and release liner as described below. The release liner is removed and discarded prior to use. See Figure 1: Figure 1: Schematic drawing of Rivastigmine Transdermal System  • a cover sheet: siliconised polyethylene terephthalate film • a backing (b) (4) Polyethylene /thermoplastic resin / aluminum coated polyester film • an active reservoir layer containing the active pharmaceutical ingredient • an adhesive matrix layer • a release liner: fluoropolymer coated polyester film Figure 1: Schematic drawing of Rivastigmine Transdermal System Coversheet Backing Film Reservoir Layer Adhesive Layer Release Liner Excipients within the formulation include colloidal silicon dioxide, light mineral oil, polyisobutylene adhesive, acrylate-vinylacetate pressure sensitive adhesive, aluminum coated polyester backing	No Changes. Please note that this proposed drug product has added labeling information to the insert/container concerning burns to the patient if the patch is left on when the patient is given an MRI. This was deemed to be acceptable since the Agency has approved applications (transdermal systems) b/f that have done so. Also, MRI's are never done while a patient is wearing any transdermal system as stated in their policy manual. Please note that the RLD does not include this information. Please note that CHEMISTRY is pending regarding the accuracy of the this section as of this review.

Table 9: Comparison of HOW SUPPLIED Section

Previously Labeling Review	Currently Proposed	Assessment
Rivastigmine Patch 4.6 mg/24 hours Each patch of 4.6 cm² contains 6.9 mg rivastigmine with <i>in-vivo</i> release rate of 4.6 mg/24 hours. Rivastigmine Patch 9.5 mg/24 hours Each patch of 9.2 cm² contains 13.8 mg rivastigmine with <i>in-vivo</i> release rate of 9.5 mg/24 hours. Rivastigmine Patch 13.3 mg/24 hours Each patch of 13.8 cm² contains 20.7 mg rivastigmine with <i>in-vivo</i> release rate of 13.3 mg/24 hours.	<u>Rivastigmine Patch: 4.6 mg/24 hours</u> Each patch of 4.6 cm² contains 6.9 mg rivastigmine with <i>in vivo</i> release rate of 4.6 mg/24 hours. Carton of 30.....NDC 47781-304-03 <u>Rivastigmine Patch: 9.5 mg/24 hours</u> Each patch of 9.2 cm² contains 13.8 mg rivastigmine with <i>in vivo</i> release rate of 9.5 mg/24 hours. Carton of 30.....NDC 47781-305-03	Firm deleted the 13.3 mg/24 hr patch since it is protected by exclusivity. Firm should add the 13.3 mg/24 hr strength back in to the How Supplied section.”

Table 10: Manufactured by statement

Previously Labeling Review	Currently Proposed	Assessment
Made in Germany Distributed by: Alvogen Pine Brook, Inc. Pine Brook, NJ 07058 USA	Made in Germany Distributed by: Alvogen, Inc. Pine Brook, NJ 07058 USA	No changes. Acceptable

8. POST APPROVAL REVISIONS

N/A

APPEARS THIS WAY ON
ORIGINAL

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 204403

Date of Submission: June 12, 2012 and January 22, 2013

Applicant's Name: Alvogen Inc.

Established Name: Rivastigmine Transdermal System, 4.6 mg/24 hr,
9.5 mg/24 hr and 13.3 mg/24 hr

Proposed Proprietary Name: None

Labeling Comments below are considered:

- NOT easily correctable (applicant cannot respond within 10 business days)
- Easily correctable (respond within 10 business days)
- No Comments (Labeling Approval Summary or Tentative Approval Summary)
-

RPM Note - Labeling comments to be sent to the firm start below:

Labeling Deficiencies determined on September 17, 2013 based on your submission dated June 12, 2012 and January 22, 2013:

1. **Carton -**

Front panel: Please utilize this sample of the RLD carton as guidance for the layout of your proposed labels. (Note the following recommendations pertain to both proposed strengths).

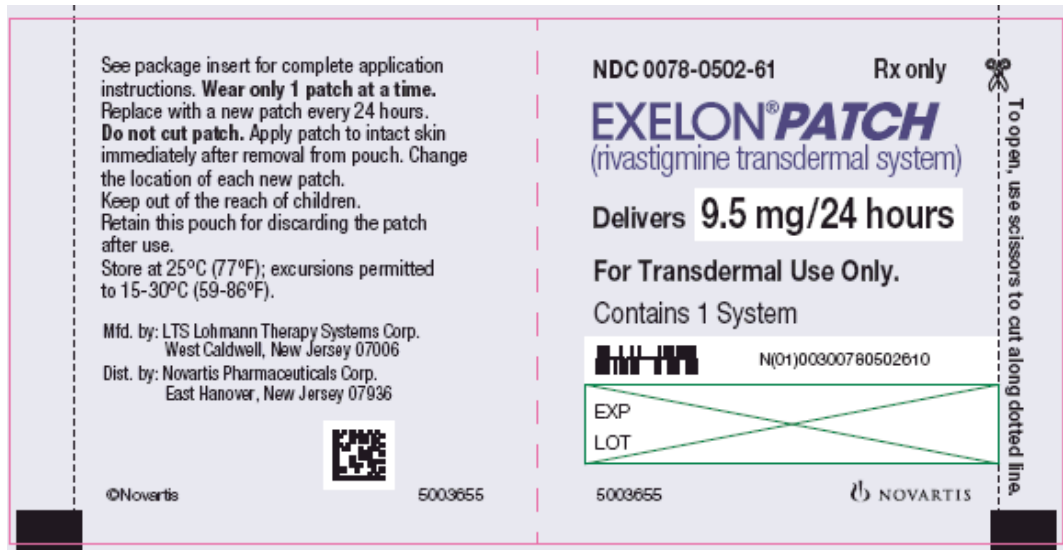
{



- a. Place the NDC # and Rx only statement at the top left and right of the label
- b.  (b) (4)
- c. Include the statement “For Transdermal Use Only” on the front panel as well as the side panel to be in accord with the RLD.

2. Individual Pouch -

Please utilize this sample of the RLD pouch as guidance for the layout of your proposed labels. (Note the following recommendations pertain to both proposed strengths).



- a. See comment 1(c.) above
- b. We note that you did not submit a pouch that included instructions and product information on the back side for the 4.6 mg/24 hr and the 9.5 mg/24 hr strength patches. Please revise and submit to be in accord with the reference listed drug.

3. Package Insert and Patient Information Leaflet

We note that revised package insert labeling has been recently approved for the reference listed drug, Exelon® Patch by Novartis (NDA 22-083/S-019; approved June 27, 2013) and these revisions are protected by exclusivity. Please address how you will certify regarding this recent update.

Patent and Exclusivity Search Results from query on Appl No 022083 Product 005 in the OB_Rx list.

Patent Data							
Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N022083	005	5602176	Feb 11, 2014	Y	Y	U - 322	
N022083	005	6316023	Jan 8, 2019		Y		
N022083	005	6335031	Jan 8, 2019		Y		

Exclusivity Data			
Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N022083	005	NPP	Jun 27, 2016
N022083	005	NS	Aug 31, 2015

Additional information:

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug's labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

Note RPM - Labeling comments end here

REMS required? No

- MedGuides and/or PPIs (505-1(e)) Yes No
- Communication plan (505-1(e)) Yes No
- Elements to assure safe use (ETASU) (505-1(f)(3)) Yes No
- Implementation system if certain ETASU (505-1(f)(4)) Yes No
- Timetable for assessment (505-1(d)) Yes No
- ANDA REMS acceptable? Yes No n/a

	Date submitted	Final or Draft	Recommendation
CONTAINER/POUCH –	6/12/12	Draft	Unacceptable
CARTON -	6/12/12	Draft	Unacceptable
BLISTER –	N/A		
PACKAGE INSERT	6/12/12	Draft	Unacceptable,

PATIENT INFORMATION/MEDICATION GUIDE	6/12/12	Draft	Unacceptable
REMS PLAN	N/A		
SPL			Not submitted

REVISIONS NEEDED POST APPROVAL? No

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER: None

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Exelon® Capsules by Novartis [NDA 022083/S-19; approved June 27, 2013].

2. USP ITEM – No (checked 9/18/13)

3. PATENTS/EXCLUSIVITIES – Firm filed for paragraph III regarding this patent.

Patent Data: 022083

Patent and Exclusivity Search Results from query on Appl No 022083 Product 005 in the OB_Rx list.

Patent Data							
Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N022083	005	5602176	Feb 11, 2014	Y	Y	U - 322	
N022083	005	6316023	Jan 8, 2019		Y		
N022083	005	6335031	Jan 8, 2019		Y		

Exclusivity Data			
Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N022083	005	NPP	Jun 27, 2016
N022083	005	NS	Aug 31, 2015

Additional information:

The firm has filed a paragraph IV to patent # 5602176 as of this submission and paragraph IV to patents #'s 6316023 and 6335031 as of the 2/27/13 submission.

When the firm filed a paragraph IV to patent #'s 6316023 and 6335031, which are patents regarding the addition of the new strength (13.3 mg/24 hr patch) as stated above. They disregarded the exclusivity for NS (New Strength) which expires 8/31/15. Therefore, this information will be included in their labeling.

See general e-mail regarding exclusivity below:

Hi Jim,

Supp 016 was approved 8/31/12 and was given 3 year exclusivity for the new potency. Supp 19 was approved June 27, 2013 and was given 3 year exclusivity.

Note exclusivities only on product 005 (the patch).

Hope this helps.

Mary Ann

From: Barlow, James T
Sent: Tuesday, September 17, 2013 1:07 PM
To: Holovac, Mary Ann
Subject: Pate3n/exclusivity question

Hi Mary Ann,

Sorry to bother you again. How about this one. New labeling was approved for NDA 022083 for Rivastigmine ex release patch

S-016 approved in March 2012

And S-019 approved June 2013

Both are efficacy supps. Did they get any exclusivity for these...Ped or other??

Thx in advance

Jim

4. DRUG PRODUCT DESCRIPTION

ANDA:

Rivastigmine Patch 4.6 mg/24 hours

Each patch of 4.6 cm² contains 6.9 mg rivastigmine with *in-vivo* release rate of 4.6 mg/24 hours.

Rivastigmine Patch 9.5 mg/24 hours

Each patch of 9.2 cm² contains 13.8 mg rivastigmine with *in-vivo* release rate of 9.5 mg/24 hours.

Rivastigmine Patch 13.3 mg/24 hours

Each patch of 13.8 cm² contains 20.7 mg rivastigmine with *in-vivo* release rate of 13.3 mg/24 hours.

RLD:

Exelon Patch: 4.6 mg/24 hours

Each patch of 5 cm² contains 9 mg rivastigmine base with in vivo release rate of 4.6 mg/24 hours.

Exelon Patch: 9.5 mg/24 hours

Each patch of 10 cm² contains 18 mg rivastigmine base with in vivo release rate of 9.5 mg/24 hours.

Exelon Patch: 13.3 mg/24 hours

Each patch of 15 cm² contains 27 mg rivastigmine base with in vivo release rate of 13.3 mg/24 hours.

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM



6. CONTAINER/CLOSURE –

All Transdermal Systems are packaged into a multi-laminate, child proof, foil pouch.

7. PACKAGING CONFIGURATIONS -

RLD: Cartons of 30

ANDA: Cartons of 30s

8. INACTIVE INGREDIENTS

Reservoir Layer (Active layer)

Rivastigmine

API

In-house monograph



9. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

NDA – Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)

ANDA – Same as RLD

10. RLD Container -



Discarding EXELON PATCH
Every 24 hours you should remove the old patch and apply a new patch.

1. Fold the used patch in half with the sticky side inwards, and place in its original pouch.
2. Discard patch safely out of the reach of children. Wash hands with soap and water.

For more information, visit
www.EXELONPATCH.com
or call 1-888-76-PATCH (1-888-767-2824).



EXELON[®]PATCH
(rivastigmine transdermal system)

Contains 30 Systems

Each 10 cm² system contains 18 mg rivastigmine to provide 9.5 mg rivastigmine every 24 hours.

Active components: acrylic copolymer; poly(butylmethacrylate, methylmethacrylate); silicone adhesive applied to a flexible polymer backing film; silicone oil; vitamin E.

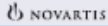
For Transdermal Use Only
Apply patch immediately after removal from pouch.
Do not store unpouched.

Keep out of the reach of children.

Do not use any patch that is damaged or shows signs of tampering.
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

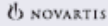
Dosage and Administration: See package insert.

www.EXELONPATCH.com @Novartis 5003656

Product of Switzerland 

EXELON[®]PATCH
(rivastigmine transdermal system)

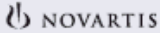
Manufactured by:
LTS Lohmann Therapy Systems Corporation
West Caldwell, New Jersey 07006

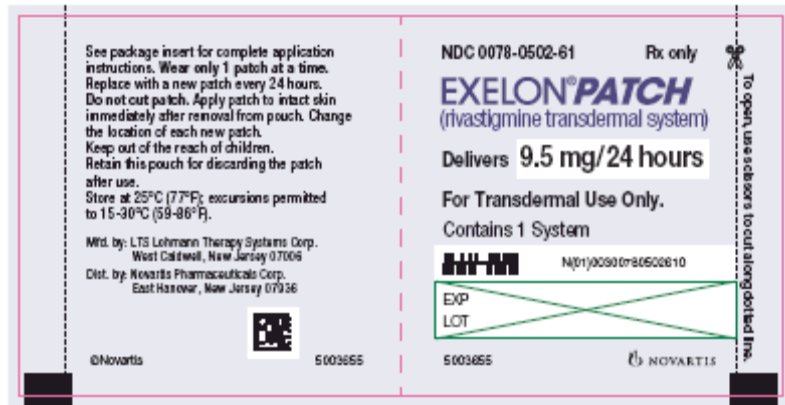
Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936 

NDC 0078-0502-15 Rx only

EXELON[®]PATCH
(rivastigmine transdermal system)
Each System Delivers 9.5 mg/24 hours
For Transdermal Use Only

Contains 30 Systems





11. **Bioequivalence** –
Unacceptable as of the 9/13/13 review.
12. Clinical Review is still deficient as per 7/16/13.

Date of Review: 9/17/13

Primary Reviewer: Jim Barlow

Team Leader: Koung Lee

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES T BARLOW
09/20/2013

KOUNG U LEE
09/24/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 204403

MEDICAL REVIEWS

**Addendum to Review of a Clinical Endpoint
Bioequivalence Study Following OSI Inspection Report**

ANDA	204403
Drug Product	Rivastigmine Transdermal System (TDS) 4.6 mg/24 hours, 9.5 mg/24 hours, and 13.3 mg/24 hours
Applicant Name	Alvogen Pine Brook, Inc.
Chemical Name	(S)- 3-[1-(dimethylamino) ethyl]phenyl ethylmethylcarbamate
Treatment Indication	Mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's disease.
Reference Listed Drug (RLD)	Exelon® Patch (rivastigmine transdermal system) 9.5 mg/24 hours
NDA	NDA 022083, approved on 7/6/07
RLD Applicant Name	Novartis Pharmaceuticals Corporation
Original Submission Date	06/12/12
Primary Reviewer	Jesse Roach MD Medical Officer Division of Clinical Review (DCR) Office of Bioequivalence (OB) Office of Generic Drugs (OGD)
Secondary Reviewer	Carol Kim, PharmD Acting ANDA Team Leader, DCR/OB/OGD
Tertiary Reviewer	Lesley-Anne Furlong, MD Acting Division Director DCR/OB/OGD
Materials Reviewed	Original Submission: 06/12/12 DCR Review prior to OSIS inspection report: 05/29/13 OSI Inspection Report: Preliminary conclusion by the Office of Study Integrity and Surveillance (OSIS) by 7/17/2015
Date of Completion	07/20/15
Conclusion	DCR recommends approval of this application. OSIS preliminary findings revealed no issues, and specifically with regard to proper recordkeeping and timing of patch application, evaluation and removal.

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Addendum to Review of a Clinical Endpoint Bioequivalence Study Following OSI Inspection Report for ANDA 204403

1 Executive Summary

This is an addendum to the original clinical review by Dr. Daiva Shetty for the ANDA 204403 completed on 5/29/2013 prior to OSIS inspection result. The original review concluded that skin irritation/sensitization and adhesion studies (study # C10-1870 and study #R10-1307) are adequate to demonstrate non-inferior skin irritation/sensitization potentials and adhesion performance between the Alvogen's Rivastigmine TDS and the reference listed drug (RLD), Exelon (Rivastigmine) TDS (NDA 022083), pending OSIS inspection result. The Division of Clinical Review (DCR) requested the Office of Study Integrity and Surveillance (OSIS), previously known as Office of Scientific Investigations (OSI), to inspect one clinical site (#2, Dr. Freeman, Cetero Research) because this site had an unsatisfactory inspectional history. In prior inspection of the same clinical site for (b) (4) which took place (b) (4) (b) (4) OSIS provided the following conclusions:

(b) (4)

Based on above findings, DCR requested a For-Cause inspection for Dr. Freeman's site #02.

The current review provides evaluation of the OSIS findings available on 7/17/15. Based on the OSIS inspection findings of site #2 (Dr. Freeman, Cetero Research), the clinical data from the study (study # C10-1870, skin irritation/sensitization study) are acceptable. The clinical data from the study #R10-1307 (adhesion study) are also acceptable per DB review dated 12/19/14.¹ No further adjustment to the study population were required based on the inspection results.

1.1 Approval Recommendation

DCR recommends approval of this application.

1.2 Summary of OSIS Inspection Report

Review of the Office of Study Integrity and Surveillance (OSIS) Preliminary Findings: 7/17/15

The OSIS completed their inspection of one clinical site (Dr. Freeman, Cetero Research). This is a summary of their preliminary findings that were communicated to this reviewer, both verbally and

¹ <http://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f8808dcb83>

by an e-mail on 7/17/2015. This was done because the final OSIS report would not be completed before the forfeiture date.

Site	PRACS Institute (Cetero Research, Principal Investigator: James C. Freeman), St. Charles, MO
Inspected records	Two-hundred-eighty (280) subjects were enrolled and two-hundred-twenty-nine completed the study. OSIS reviewed 70 subjects records.
Inspection findings	There were no issues found during the inspection. There were no discrepancies between paper records and computerized records. Adverse events were properly recorded. Investigative records were all present and the study report was found to be an accurate representation of the on-site study records.
e-mail communication by OSIS dated 7/17/15 (Nicola Fenty-Stewart)	“Record review included: comparison of background data provided with the assignment against the site protocol, case report forms and source documents; subject informed consent forms, study correspondence, study product randomization and handling; handling, processing, storage and shipment, final study report to the Institutional Review Board (IRB) and adherence to written SOPs. From the subject records that were reviewed, there were no protocol deviations regarding the timing of application of skin patches, removal of patches and evaluation of skin irritation.” See appendix for details.

Reviewer’s Comments: *Based on above communication provided by the OSIS to DCR, the inspection results are satisfactory to this reviewer. The concerns about this clinical site (#2) were addressed and found to be satisfactory by OSIS investigators, specifically with regard to timing of evaluations and placement and removal of patches and proper investigative recordkeeping. Thus, study data are acceptable for the review.*

2 Additional Clinical Review

2.1 Review of the FDA Statistical Report

Per OSIS inspection findings of 7/17/15, no further subject adjustment is needed.

2.2 Conclusion and Recommendation

2.2.1 Conclusion

Following the OSIS inspection findings dated 7/17/15, the clinical data (study # C10-1870 and study #R10-1307) submitted to ANDA 204403 are adequate to demonstrate non-inferior skin irritation and sensitization potentials and adhesion performance of Alvogen’s Rivastigmine TDS to the RLD, Exelon (Rivastigmine) TDS.

2.2.2 Recommendation

DCR recommends approval of this application, contingent on approval recommendations from the other disciplines on the review team.

APPEARS THIS WAY ON
ORIGINAL

CLINICAL BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

The Division of Clinical Review has no comments.

APPEARS THIS WAY ON
ORIGINAL

Appendix: Email Communication

From: Fenty-Stewart, Nicola
Sent: Friday, July 17, 2015 12:28 PM
To: Roach, Jesse
Cc: Dasgupta, Arindam
Subject: RE: 204403 OSIS inspection

Hi Jesse,

Here is the information that we have from the investigator:

Record review included: comparison of background data provided with the assignment against the site protocol, case report forms and source documents; subject informed consent forms, study correspondence, study product randomization and handling; handling, processing, storage and shipment, final study report to the Institutional Review Board (IRB) and adherence to written SOPs. From the subject records that were reviewed, there were no protocol deviations regarding the timing of application of skin patches, removal of patches and evaluation of skin irritation.

Let me know if you need anything else.

Thanks,
Nicola

From: Roach, Jesse
Sent: Friday, July 17, 2015 11:52 AM
To: Fenty-Stewart, Nicola
Subject: RE: 204403 OSIS inspection

Hello- One more thing about the inspection. Did the inspectors comment on the timing of placement and reading of results. One of the reasons the inspection was requested was because on a previous ANDA there were deviations from the protocol in timing of skin evaluations.

Thanks

Jesse

Jesse Roach, MD
Medical Officer, Division of Clinical Review
Office of Generic Drugs
White Oak Bldg 75, Room 2508
(240) 402-3219
Jesse.Roach@fda.hhs.gov

Clinical Review of ANDA 204403

Skin Irritation/Sensitization and Adhesion Studies

Drug Product:	Rivastigmine Transdermal System (TDS) 4.6 mg/24 hours, 9.5 mg/24 hours, and 13.3 mg/24 hours
Drug Class:	Cholinesterase Inhibitor Drugs for Memory (Alzheimers/Senility/Dementia) (2013060)
Chemical Name:	(S)- 3-[1-(dimethylamino) ethyl]phenyl ethylmethylcarbamate
ANDA:	204403
ANDA Sponsor:	Alvogen Pine Brook, Inc.
Reference Listed Drug:	Exelon® Patch (rivastigmine transdermal system) 9.5 mg/24 hours
NDA:	NDA 022083, approved 7/6/07
RLD Sponsor:	Novartis Pharmaceuticals Corporation
Reviewer:	Daiva Shetty, M.D. Medical Officer, Division of Clinical Review (DCR) Office of Generic Drugs
Secondary Reviewer:	John R Peters, M.D. Director, Division of Clinical Review Office of Generic Drugs
Tertiary Reviewer:	Ethan M. Stier, Ph.D., R.Ph. Director, Division of Bioequivalence II Office of Generic Drugs
Materials Reviewed:	ANDA 204403 submissions dated June 12, 2012, January 3, 2013, January 22, 2013 Relevant information from the NDA 022083 Statistical Review entered in DARRTS 5/28/2014 OSI inspection report Regulatory history of Rivastigmine
Date of Submission:	June 12, 2012
Addenda to submission:	January 3, 2013, January 22, 2013
Date of Completion:	May 29, 2013
Conclusion:	Submitted data demonstrated that the generic patch is no more irritating, no more sensitizing and adheres at least as well as the RLD Exelon patch. From the clinical safety perspective, ANDA 204403 should be approved, pending satisfactory OSI inspection, CMC, Labeling, comparative bioavailability data, and any other relevant regulatory assessment. There were multiple deficiencies noted in the CMC review with the final recommendation for the Complete Response Action. If deficiencies listed in the CMC review will require reformulation of the patch, data from the two clinical safety studies may not be applicable and the sponsor may need to repeat those studies.

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1 Executive Summary

Rivastigmine is a (b) (4) cholinesterase inhibitor, indicated for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's disease. It was originally approved by FDA as an immediate-release capsule (NDA 020823) and oral solution (NDA 021025) formulations on March 21, 2000. A transdermal formulation of rivastigmine was approved on July 6, 2007 (NDA 022083).

On June 12, 2012, Alvogen Pine Brook, Inc. (Alvogen) submitted an abbreviated new drug application (ANDA) requesting approval to market a generic Rivastigmine Transdermal System (TDS) for the reference listed drug (RLD) Exelon® Patch, NDA 022083. The RLD patch is approved in three different strengths: 4.6 mg/24 hours, 9.5 mg/24 hours, and 13.3 mg/24 hours. Alvogen initially proposed to market only the two lower strengths of the patch - 4.6 mg/24 hours, 9.5 mg/24 hours. On June 22, 2013, Alvogen submitted an amendment to their ANDA requesting approval to market the 13.3 mg/24 hours patch as well.

In support of their application, Alvogen provided CMC, clinical pharmacology, as well as clinical safety data. The development program for this product was based on the OGD's draft guidance on transdermal rivastigmine (Recommended February 2010, Revised June 2010, November 2010, and November 2013). This review evaluated clinical data from the following two clinical studies:

1. Skin irritation and sensitization study #C10-1870 (R10-1318, S11-0069)
2. Bioavailability and adhesion assessment study #R10-1307

Summary of finding from the skin irritation and sensitization study #C10-1870

This was a skin irritation/sensitization study with the 21 day Induction phase followed 14 days later by the Challenge phase. The design and methods of the study were consistent with the FDA's Draft Guidance on Rivastigmine. As recommended by the Draft Guidance, one-half cut patch of the 4.6 mg/24 hour test formulation and one-half cut patch of the 4.6 mg/24 hour reference formulation was applied.

A total of 280 subjects were enrolled, and 262 completed the Induction phase of the study. Overall, data showed similar trends in frequency and severity of irritation scores for the test and the RLD patches.

The majority of the study subjects developed irritation to the tested patches over the 21-day Induction phase. By Day 22, 256 (97.7%) out of 262 subjects in both treatment arms had at least a score of 1 for irritation, almost half of the study population developed a score of 2 (45.2% for the Test Product A and 47.7% for the Reference Product B). There was no difference between the treatment arms in the percentages of subjects developing irritation by scores of severity. The means of cumulative irritation scores were similar in both treatment arms, 32.02±18.57 for the Test Product A vs. 32.5±17.64 for the Reference Product B.

The number of subjects that required the patch to be moved due to irritation was similar in both treatment groups. The number of subjects discontinuing the study due to local irritation

was relatively low (N=26); none of those discontinuations were due to excessive irritation in the Challenge phase.

The per-protocol population for sensitization for the Challenge Phase included 229 of 230 subjects for Test Product A and 228 of 230 subjects for Reference Product B.

Forty-three subjects (43/228 or 18.9%) demonstrated a possible sensitization reaction to both transdermal systems in the Challenge Phase. Of the 43 subjects, no subject demonstrated a possible sensitization reaction for only the Test Product or only the Reference Product. Most developed mild irritation. Only three subjects in the Test treatment and four subjects in the Reference treatment arm developed irritation scores of 4-5.

The FDA statistician stated that the non-inferiority analyses based on the mean cumulative irritation scores (primary endpoint) showed that the - 95% upper confidence limit (UCL) for the adjusted mean difference ($\mu_T - 1.25\mu_R$) was less than zero (-0.3728). The non-inferiority test passed therefore the irritation potential of the test patch is considered no worse than that of the reference patch. The FDA statistician also stated that the test patch might exceed the reference patch by at most 1.3 percentage points based on the 95% upper confidence limit for the difference in sensitization rates. Overall conclusion by the statistician was that the test patch was found to be non-inferior to the reference patch for irritation and sensitization.

Summary of findings from the bioavailability and adhesion assessment study R10-1307

This was a randomized, single-dose, 2-period, 2-treatment, open-label crossover bioavailability and adhesion study conducted under fasting conditions. The design and methods of the study were consistent with the FDA's Draft Guidance on Rivastigmine. Treatment arms consisted of single doses of rivastigmine 9.5 mg/24 hours patch and the Exelon 9.5 mg/24 hours patch. The adhesion assessment scale used in the study was consistent with the one recommended in the draft guidance.

A total of 30 subjects were enrolled and 27 completed the study. The proportion of subjects developing a score of at least 1 for detachment was similar for the test product compared to the RLD (6 vs. 7 subjects). Only one subject developed a score of 2 in the Test Product A arm. This degree of detachment is not clinically significant. There was no difference between the treatments how early into the treatment the detachment occurred; both treatment arms had the first subject with the score of 1 at the 8th hour.

The initial FDA analysis was performed using methods recommended in the Draft Guidance on Rivastigmine. Following conclusion was made by the reviewer: "Non-inferiority analyses based on the mean cumulative adhesion scores (primary endpoint) showed that the one-sided 95% upper bound for confidence limit for the adjusted mean difference ($\mu_T - 1.25\mu_R$) was greater than zero and the non-inferiority test was not passed for test versus reference patch. Therefore, the adhesion potential of the test is not non-inferior to that of the reference."

However, based on the memo for statistical non-inferiority analysis for highly adhering patch drug products the adhesion data in the study R10-1307 was reconsidered. The FDA statistician concluded that on average 90% of the test patches and 92% of the reference patches had $\geq$ 90% adhesion for the study duration. The products met or exceeded the

adhesion criterion of 90/90 ($\geq 90\%$ of patches having $\geq 90\%$ adhesion throughout the entire study). Therefore, the study passed the adhesion waiver requirement. However, the sample size (27 subjects) did not meet the recommendation of a minimum of 60 subjects.

Safety

The study R10-1307 was not designed as a safety study. However, data on adverse events was collected during the course of the study. A total of 310 subjects were exposed to the generic rivastigmine patch: 280 subjects in the skin irritation/sensitization study C10-1870 and 30 subjects in the bioavailability study R10-1307.

Study C10-1870

All subjects in this study simultaneously received a half patch application of each treatment (test product rivastigmine patch and the RLD Exelon® patch) 4.6 mg/24 hours for 21 consecutive days and again, after 14-day rest period, the same treatment once for 48 hours.

No SAEs were reported over the course of this study. One subject was discontinued and one subject withdrew from the study due to AEs. One subject was discontinued due to a positive urine pregnancy test result.

Since both treatments were administered at the same time, most adverse events could not be attributed to a specific treatment, except for application site disorders. Overall, skin reaction AEs (application site discharge, application site irritation, application site pain, and application site pruritus) were reported by 75 (75/280) subjects (26.79%) and 69 (69/280) subjects (24.64%) during treatment with Rivastigmine TDS, 4.6 mg/24 hours and Exelon Patch, 4.6 mg/24 hours, respectively.

Headache, oropharyngeal pain, and rhinorrhea were each reported on 1 occasion in 8 (8/280) subjects (2.86%), nasopharyngitis was reported on 1 occasion in 3 (3/280) subjects (1.07%); other AEs reported by 3 or more subjects were abdominal pain, diarrhea, nausea, fatigue, dizziness, somnolence, and insomnia.

Study R10-1307

A total of 30 subjects were enrolled and 27 completed the bioequivalence study R10-1307. Safety population included all 30 subjects.

No serious adverse events (AEs) were reported over the course of this study. Overall, the most common AEs reported were nausea (7 (23.3%) subjects), headache (4/30 (13.33%) subjects), vomiting (3 (10%) subjects), and abdominal discomfort (2 (6.67%) subjects). All of these events were considered by the Investigator to be possibly or likely related to the treatments. There was no difference in the number or type of AEs reported between the two treatment arms. Only nausea was reported more frequently in the reference treatment arm. None of the study subjects developed local skin irritation.

Overall Conclusion

Clinical safety data from two clinical studies C10-1870 and R10-1307 submitted to support ANDA 204403 provided sufficient evidence that the proposed Rivastigmine TDS is safe and non-inferior to the RLD Exelon® patch in its irritation/sensitization potential. It is also non-

inferior in its patch adhesion performance. Submitted data demonstrated that the generic patch is no more irritating, no more sensitizing and adheres at least as well as the RLD Exelon patch. Even though the skin irritation/sensitization study evaluated only the lower strength (4.6 mg/24 hours) of the patch, there is no reason to believe that the higher strengths would have a different dermal safety profile. Adhesion assessment was done only for the 9.5 mg/24 hours patch. Since all three strengths of the proposed patches are proportionally similar in their formulation, safety and adhesion data can be extrapolated to all three strengths.

1.1 Recommendation on Approval

From the clinical safety perspective, ANDA 204403 should be approved, pending satisfactory OSI inspection, CMC, Labeling, comparative bioavailability data, and any other relevant regulatory assessment.

There were multiple deficiencies noted in the CMC review (entered in DARRTS on 3/7/2014) with the final recommendation for the Complete Response Action. If deficiencies listed in the CMC review will require reformulation of the patch, data from the two clinical safety studies may not be applicable and the sponsor may need to repeat those studies.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

Alvogen submitted ANDA 204403 proposing to market a generic formulation of a transdermal formulation (TDS) of rivastigmine. To support the application, Alvogen conducted a skin irritation and sensitization study, enrolling 280 subjects to compare irritation/sensitization potential of their Rivastigmine TDS to those of the RLD Exelon®. In addition, Alvogen conducted a bioavailability study in 30 subjects where they also assessed a patch adhesion properties.

This review evaluated data from the skin irritation/sensitization study C10-1870 as well as safety and patch adhesion data from the bioavailability study R10-1307.

1.2.2 Comparative Irritation Conclusion

Based on the statistical analysis, the non-inferiority analyses based on the mean cumulative irritation scores (primary endpoint) showed that the - 95% upper confidence limit (UCL) for the adjusted mean difference ($\mu T - 1.25\mu R$) was less than zero (-0.3728). The non-inferiority test passed therefore the irritation potential of the test patch is considered no worse than that of the reference patch.

1.2.3 Comparative Sensitization Conclusion

The Sponsor provided sufficient evidence that sensitization potential of Alvogen's Rivastigmine TDS is not worse than that of the RLD Exelon® patch. The FDA statistician analysis showed that the test patch might exceed the reference patch by at most 1.3

percentage points based on the 95% upper confidence limit for the difference in sensitization rates. Overall conclusion by the statistician was that the test patch was found to be non-inferior to the reference patch for irritation and sensitization.

1.2.4 Comparative Adhesion

The adhesion performance of the patch is acceptable. Data from the study #R10-1307 demonstrate that there is no difference in adhesion properties between the new proposed generic patch and the RLD Exelon® patch. The FDA statistician concluded that on average 90% of the test patches and 92% of the reference patches had $\geq 90\%$ adhesion for the study duration. The products met or exceeded the adhesion criterion of 90/90 ($\geq 90\%$ of patches having $\geq 90\%$ adhesion throughout the entire study). Therefore, the study passed the adhesion waiver requirement. However, the sample size (27 subjects) did not meet the recommendation of a minimum of 60 subjects.

1.2.5 Comparative Safety

Overall, AEs reported during the Alvogen's drug development program are consistent with the side effects reported with topical application of Rivastigmine. There was no difference in frequency, severity, or the type of AEs reported between the proposed generic Rivastigmine patch and the RLD.

2 Clinical Review

2.1 Introduction and Background

Rivastigmine is a (b) (4) cholinesterase inhibitor, indicated for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's disease. It was originally approved by FDA as an immediate-release capsule (NDA 020823) and oral solution (NDA 021025) formulations on March 21, 2000. A transdermal formulation of rivastigmine was approved on July 6, 2007 (NDA 022083).

The efficacy of the Exelon® Patch (rivastigmine) transdermal system has been established in controlled efficacy trials. Several different size patches were studied by the innovator during drug development. It was noted that the incidence of specific, common, mainly gastrointestinal, adverse events was higher in those assigned to the highest strength (17.4 mg/24 hours) patch than in those assigned to the lower strengths. The most common adverse events (AEs) reported during the RLD development were: nausea, vomiting, diarrhea, anorexia/decreased appetite, and weight loss. Dehydration may result from prolonged vomiting or diarrhea and can be associated with serious outcomes. The incidence and severity of these reactions are dose-related. For this reason, labeling recommends initiating treatment with Exelon® Patch at a dose of 4.6 mg/24 hours and titrate to a dose of 9.5 mg/24 hours and then to a dose of 13.3 mg/24 hours, if appropriate¹.

¹ Information from the approved Exelon® labeling.

Alvogen Pine Brook, Inc. (Alvogen) submitted ANDA requesting approval to market a generic Rivastigmine Transdermal System (TDS) for the reference listed drug (RLD) Exelon® Patch, NDA 022083. The RLD patch is approved in three different strengths: 4.6 mg/24 hours, 9.5 mg/24 hours, and 13.3 mg/24 hours. Alvogen initially proposed to market only the two lower strengths of the patch - 4.6 mg/24 hours, 9.5 mg/24 hours. On June 22, 2013, Alvogen submitted an amendment to their ANDA requesting approval to market the 13.3 mg/24 hours patch.

2.1.1 Summary of Drug Information

Table 1: Drug Information

Drug Established Name	Rivastigmine Transdermal System 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr
Drug Class	Drugs for Memory (Alzheimers/Senility/Dementia) (2013060) Cholinesterase Inhibitor
Reference Listed Drug	Exelon® Patch
RLD Firm	Novartis Pharmaceuticals Corporation
NDA #	022083
Date of RLD Approval	7/6/2007
Approved Indication(s)	For treatment of : • Mild to moderate dementia of the Alzheimer’s type • Mild to moderate dementia associated with Parkinson’s disease
Recommended Dosing Regimens	• Apply patch on intact skin for a 24-hour period; replace with a new patch every 24 hours • Initiate treatment with 4.6 mg/24 hours Exelon Patch • After a minimum of 4 weeks, if tolerated, increase dose to 9.5 mg/24 hours, which is the minimum effective dose • Following a minimum additional 4 weeks, may increase dosage to maximum dosage of 13.3 mg/24 hours • For treatment interruption longer than three days, re-titrate dosage starting at 4.6 mg/24 hours

2.1.2 Regulatory Background

This application is submitted under the 505(j) Section of the Federal Food, Drug and Cosmetic Act referencing NDA 022083 for the Exelon® patch.

To date, one NDA (see Table 1), six ANDAs (see Table 2), and no commercial INDs are listed in DARRTS for rivastigmine transdermal patch. There is no unexpired exclusivity for

the two lower strengths of the patch. There is an unexpired exclusivity for the latest approved new strength 13.3 mg/24 hr until August 31, 2015.

Table 2: NDAs for Rivastigmine Patch (n=1)

Appl No	TE Code	RLD	Approved	Marketing Status; Regulating Division	Active Ingredient	Dosage Form; Route; Strength	Proprietary Name	Applicant
NDA-022083		Yes*	07/06/2007**	Prescription; DNP***	Rivastigmine	PATCH 4.6 MG/24HR 9.5 MG/24HR 13.3MG/24HR	EXELON PATCH	NOVARTIS PHARMACEUTICALS CORP

Source: Search by reviewer of the Agency Document Archiving, Reporting & Regulatory Tracking System (DARRTS), Drugs@FDA and the Orange Book conducted on 5/23/13. TE=Therapeutic Equivalence; RLD=Reference Listed Drug
*Only 9.5 mg/24 hr is listed as RLD; **4.6 mg/24 hr and 9.5 mg/24 hr were approved on 7/6/07, 13.3 mg/24 hr was approved on 8/31/12; ***DNP - Division of Neurology Products

2.1.2.1 INDs, Protocols, or Control Documents submitted by Sponsor

There were no INDs, protocols, or controlled correspondences submitted by this sponsor.

Alvogen initially proposed to market only two lower strengths of the patch - 4.6 mg/24 hours, 9.5 mg/24 hours. On June 22, 2013, Alvogen submitted an amendment to their ANDA requesting approval to market the 13.3 mg/24 hours patch. At the time of filing of this ANDA, several deficiencies were noted and information requests were sent to the sponsor. Pertinent to this review, source documents, datasets, and some additional analyses were requested for the irritation and sensitization study. The Sponsor submitted all of the requested information on January 3, 2013.

2.1.2.2 Other ANDA submissions for same product

Table 3: ANDAs for Rivastigmine Patch (n=6)

Appl No	TE Code	RLD	Marketing Status; Regulating Division	Active Ingredient	Dosage Form; Route; Strength	Applicant
(b) (4)						
ANDA-205622		No	Pending 04/25/2013 OGD	RIVASTIGMINE	PATCH	MYLAN TECHNOLOGIES INC
ANDA-204403		No	Pending 06/12/2012 OGD	RIVASTIGMINE	PATCH	ALVOGEN INC
(b) (4)						

Appl No	TE Code	RLD	Marketing Status; Regulating Division	Active Ingredient	Dosage Form; Route; Strength	Applicant
(b) (4)						

Source: Search by reviewer of the Agency Document Archiving, Reporting & Regulatory Tracking System (DARRTS), Drugs@FDA and the Orange Book conducted on 5/23/13. TE=Therapeutic Equivalence; RLD=Reference Listed Drug

2.1.3 Other Relevant Information

OGD published an Individual Product Bioequivalence Recommendations: Draft Guidance on transdermal rivastigmine (Recommended February 2010, Revised June 2010, November 2010, and November 2013)². An outline of the recommendations in the draft guidance is listed in Appendix 1 of this review.

To date, 16 Controlled Correspondences (see Table 3) and no protocols have been submitted to the OGD for rivastigmine transdermal patch.

Table 4: OGD Controlled Correspondences re: Rivastigmine Transdermal Patch
(n=16: 11 closed; 3 open; 1 deleted)

Ctl No	Description	(b) (4)
08-0180	BE recommendations/ requirements	
08-0189	Request for BE and dissolution recommendations	
08-0231	BE studies and guidance.	
08-0526	BE/dissolution method recommendations	
10-0037	Requesting Pre-ANDA meeting.	
10-0371	Request for TDS irritation and sensitization study	
10-0716	Requesting formulation guidance.	
10-0729	Requesting guidance in the development of this product.	
10-0749	Request for proposed formulation guidance.	
11-0107	Questions regarding this	

²

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201278.pdf>

Ctl No	Description	(b) (4)
	product.	
12-0205	Requesting study guidance. Opinion on the acceptability of the conduct of this study entirely at the Montreal site.	
12-0355	Inactive Ingredient Review Plastiod B; Silicone Adhesive 4302 and Silicone Oil in Rivastigmine Extended release Transdermal Patch:	
12-0355A	Inactive Ingredient Review Silicone Adhesive 4302 in Rivastigmine Extended release Transdermal Patch:	
12-0937	BE Guidance/ Recommendation Rivastigmine Extended Release Transdermal Film	
12-1102	Inactive Ingredient Review Rivastigmine Transdermal System - labeling MRI warning statement - Scotchpak 1109 backing Initially assigned to label	
13-0251	Inactive Ingredient Review Silicone Adhesive 4302 in Rivastigmine Extended release Transdermal Patch: Per RSB - this should be looked at by chemistry	

Source: Search by reviewer of the OGD Tracking Systems, Internal Document Tracking, Controlled Correspondence Database conducted on 5/23/13. Ctl=Control; No=Number; Doc=Document; Req=Request; L=Letter (or e-mail)

Pertinent to this review is Control #12-0937 submitted by (b) (4) requesting guidance on marketing the highest strength of rivastigmine topical patch, 13.3 mg/24 hours. At the time the Draft Guidance on transdermal rivastigmine was written, there were only two strengths of RLD patch approved, 4.6 mg/24 hr and 9.5 mg/24 hr. On April 29, 2013, the Division of Clinical Review (DCR) completed a consult from the Division of Bioequivalence II (DB II) for this control. In summary, DCR recommended the following:

- The 9.5 mg/24 hr patch should remain designated as RLD for this product
- The other two remaining dosage strengths may qualify for a waiver of bioequivalence testing requirements for the test product if the following conditions are met:
 - a) acceptable bioequivalence study on the RLD strength
 - b) acceptable dissolution testing of all strengths
 - c) proportional similarity in the formulations across all strengths
- As currently recommended in the posted Draft Guidance for Rivastigmine Transdermal System (latest revision dated November 2010), requesting a pharmacokinetic BE study on 9.5 mg/24 hours strength patch in healthy volunteers is appropriate for determination of bioequivalence of this product

- If the test formulation of 13.3 mg/24 hours is proportionally the same to their lower strength products, no additional skin irritation/sensitization/adhesion study on the highest strength product, 13.3 mg/24 hours are recommended. Current recommendation of using ½ of 4.6 mg/24 hours patch strength is sufficient and considered the lowest safe dosage for evaluation of skin irritation/sensitization potential of this product.
- A separate adhesion performance between products on the recommended RLD, 9.5 mg/24 hours, is also recommended.

The OGD's draft guidance on rivastigmine has been updated on November 2013 to include these recommendations.

2.2 Description of Clinical Data and Sources

In support of their application, Alvogen provided data from the following two clinical studies:

1. Skin irritation and sensitization study #C10-1870 (R10-1318, S11-0069)
2. Bioavailability and adhesion assessment study #R10-1307

Patch Skin Irritation/Sensitization Study (Study C10-1870 (R10-1318, S11-0069))

Study Title	A Multiple Site Study to Evaluate the Irritation and Sensitization Potential of Repeat Applications of Rivastigmine 4.6 mg/24 hours Patch (Transdermal System) versus Exelon 4.6 mg/24 hours Patch (Rivastigmine Transdermal System) in Normal Healthy Volunteers
Protocol Number	Study C10-1870 (R10-1318, S11-0069)
CRO	Cetero Research
Study Period	
First Subject Enrolled	16 January 2012 (date of first patch application for Induction Phase)
Last Subject Completed	25 February 2012 (date of last evaluation for Challenge Phase)
Study Centers, Principal Investigators and Enrollment	
Site #01	Alan K. Copa, PharmD
Site #02	James C. Freeman, MD

Patch Adhesion Study (Study R10-1307)

Study Title	A Study to Evaluate the Relative Bioavailability and Adhesive Properties of Rivastigmine 9.5 mg/24 hours Patch (Transdermal System) versus Exelon 9.5 mg/24 hours Patch (Transdermal System) in Normal Healthy Volunteers
Protocol Number	R10-1307
CRO	Cetero Research
Study Period	
Study Initiation Date	November 12, 2011
Study Completion Date	November 20, 2011
Study Centers, Principal Investigators and Enrollment	
Site #1	Anthony R. Godfrey, Pharm. D.

2.3 Clinical Review Methods

2.3.1 Overview of Materials Consulted in Review

Original Submission:

The original submission of this application dated 6/11/2012, received by FDA 6/12/2012 contained the following:

- Chemistry, manufacturing and controls data
- Clinical pharmacology data
- Clinical and statistical data
- Financial disclosure certification
- Patent and Exclusivity certifications
- Labeling

A major amendment to this ANDA was submitted on January 12, 2013 requesting to market an additional strength of the patch, 13.3 mg/24 hours. This amendment included additional chemistry and manufacturing information, in-vitro dissolution data, as well as updated labeling. There were no additional clinical data submitted.

This review will evaluate the skin irritation and sensitization study #C10-1870 (R10-1318, S11-0069) as well as safety and patch adhesion data gathered in the bioavailability study #R10-1307.

Study Amendments:

There were no amendments to the studies after their initiation.

Additional responses to requests for information from FDA were submitted. Following are the additional submissions recorded in DARRTS:

- DARRTS sequence 0001 (10/19/2012) - the Sponsor provided cGMP statement.
- DARRTS sequence 0002 (1/3/2013) – the sponsor responded to deficiencies noted in the filling letter. Pertinent to this review, source documents, datasets, and some additional analyses were provided in this submission for the irritation and sensitization study.
- DARRTS sequence 0003 (1/22/2013) - a major amendment to this ANDA requesting to market an addition strength of the patch, 13.3 mg/24 hours.
- DARRTS sequence 0004, 005, and 006 (1/18/2013, 1/18/2013, 2/27/2013) – information on patent certifications were provided
- DARRTS sequence 0007 (4/11/2013) – amendment to bioequivalence testing, revised dissolution apparatus and methods.
- DARRTS sequence 0008 (4/22/2013) – response to the “Acceptable for filing amendment” – additional CMC and administrative information provided. No clinical data were included.
- DARRTS sequence 0009 (5/2/2013) – revised bioequivalence methods provided.

2.3.2 Overview of Methods Used to Evaluate Data Quality and Integrity

Division of Scientific Investigations (DSI) Report:

There were two clinical sites for the skin irritation/sensitization study #C10-1870:

Site 01: Dr. Alan K. Copa

Site 02: Dr. James C. Freeman

OSI inspection was not requested for the Site 01 because of a satisfactory prior inspection history on the same site (ANDA 202346, Lidocaine Topical Patch, 5%).

Site 02 has an unsatisfactory inspection history [REDACTED] (b) (4). On May 21, 2013, OSI provided their evaluation of the FDA audit of the clinical portions of two studies for [REDACTED] (b) (4), conducted at PRACS Institute (Cetero Research, Principal Investigator: James C. Freeman), St. Charles, MO, during [REDACTED] (b) (4) by ORA investigators Kathleen B. Swat and Karen M. Montgomery (Kansas District Office). OSI provided the following conclusions:

[REDACTED] (b) (4)

Because of these findings, DCR requested a For-Cause inspection for Dr. James C. Freeman (Site #02). Results of this inspection are pending at this time.

2.3.3 Were Trials Conducted in Accordance with Accepted Ethical Standards

The Sponsor provided a statement that both clinical studies were performed in accordance with all applicable Good Clinical Practice guidelines, including archiving of essential documents (ICH E6 [R1], June 1996).

The protocol #C10-1870 dated December 27, 2011 and the consent form dated December 27, 2011 were approved by the PRACS Institute, Ltd. Institutional Review Board (IRB) on January 4, 2012, prior to study commencement.

The protocol #R10-1307 and the consent form dated November 4, 2011 were approved by the PRACS Institute, Ltd. Institutional Review Board (IRB) on November 9, 2011, prior to study commencement.

2.3.4 Evaluation of Financial Disclosure

[REDACTED] (b) (6) had two study sites and two principal investigators: [REDACTED] (b) (6) [REDACTED] (b) (6) [REDACTED] (b) (6) was conducted at one site by one principal investigator [REDACTED] (b) (6) and 12 sub-investigators.

The sponsor provided financial disclosure statement (FDA form 3454) certifying that they did not enter into any financial arrangements with the two out of three principal investigators (b) (6) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

Reviewer's Comment: *There are two study sites and two principal investigators for the (b) (6) FDA financial disclosure form 3454 mentions only (b) (6) information request was sent to the Sponsor asking them to provide the financial disclosure statement for (b) (6). In their response on 6/12/2013 the Sponsor stated that the financial certificate for (b) (6) is provided in the original submission of the study (b) (6) report. The financial disclosure is provided not in the FDA 3454 form, but in the (b) (6) form. For the purposes of this review, this is acceptable.*

2.4 Review of Skin Sensitization, Irritation, and Adhesion Studies

2.4.1 Brief Statement of Conclusions

The statistical review conducted by Dr. Guoying Sun confirms the adequacy of data to determine that the irritation and sensitization potential of the sponsor's product are not inferior to those of Exelon® patch. The data also demonstrate that adhesion performance of the proposed generic rivastigmine patch is acceptable.

2.4.2 General Approach to Review of the Comparative Efficacy of the Drug

There were no comparative efficacy trials for the proposed generic drug product. To support the comparative efficacy of the drug, the Sponsor submitted the following:

1. Bioequivalence data for the 9.5 mg/24 hr patch
2. Dissolution data for all three strengths of the patch
3. Proportional similarity of the formulations
4. Topical safety (irritation and sensitization) and patch adhesion data

2.4.3 Detailed Review of the Patch Skin Irritation and Sensitization Study (Study C10-1870 (R10-1318, S11-0069))

2.4.3.1 Protocol

Sponsor's protocol#:	C10-1870 (R10-1318, S11-0069)
Title	A Multiple Site Study to Evaluate the Irritation and Sensitization Potential of Repeat Applications of Rivastigmine 4.6 mg/24 hours Patch (Transdermal System) versus Exelon 4.6 mg/24 hours Patch (Rivastigmine Transdermal System) in Normal Healthy Volunteers

Objectives	To confirm that the test product is no more irritating and sensitizing than the reference product when applied over a continuous 21 day Induction Phase followed by a 48 hour Challenge Phase

2.4.3.1.1 Study Design

This study was multiple-site, randomized, multiple application, evaluator-blinded, controlled, in vivo, within-subject test.

Treatments

Test Articles

As recommended by the FDA’s Draft Guidance on Rivastigmine, one-half cut patch of the 4.6 mg/24 hour test formulation and one-half cut patch of the 4.6 mg/24 hour reference formulation was applied to the upper arms during the Induction Phase and to separate sites on the upper back during the Challenge and Re-Challenge Phases. Treatment consisted of the following:

Treatment Code	Description
A	Rivastigmine Transdermal System, 4.6 mg/24 hours*
B	Exelon 4.6 mg/24 hours Patch (Rivastigmine Transdermal System)**

* Patch manufactured by (b) (4) (Lot No. C0002AL0AT); **Patch manufactured by LTS Lohmann Therapy Systems Corp.

Subjects were assigned to their subject number and corresponding randomization in the order in which they entered the study. During the Irritation/Induction Phase, the patches were applied to the upper arms on Days 1 through 21. Sensitization application started on Day 36. The same treatment sequence that was applicable during the Irritation/Induction Phase was applied during the Sensitization/Challenge Phase but to skin sites on the upper back. The patches applied for the sensitization evaluation were removed after 48 hours ± 4 hours by study staff other than the person who scored the sites.

Reviewer’s Comment: *The study design is consistent with the recommendations in the draft guidance for rivastigmine patch. Selection of the products for testing, one-half cut of the generic and one-half cut of the RLD patch, was possible because both patches have a matrix design. Application of two half-cut patches is recommended by the draft guidance due to safety concerns, to avoid high exposure to rivastigmine over the 21-day study duration.*

Study Population:

Inclusion Criteria

Volunteers who met the following criteria were included as subjects in the study.

1. Informed of the nature of the study, agreed to, and were able to read, review, and sign the informed consent document prior to Day 1 patch application. The informed

consent document was written in English, therefore the volunteer must have had the ability to read and communicate in English.

2. Completed the screening process within 28 days prior to Day 1 patch application.
3. Male or female, 18 – 65 years of age, inclusive, at the time of Day 1 patch application.
4. Judged by an Investigator on the basis of pre-study medical history, vital sign assessment, and ECG to have no health conditions that would impact the safety of the subject during participation.
5. Willing to shower using the same soap/cleansers between the Screening Visit and the end of the study.
6. Willing to follow study restrictions.
7. Females were:
 - of childbearing potential and practicing an acceptable method of birth control as judged by the Investigator(s); or,
 - naturally postmenopausal (no menses) for at least 2 years and were at least 45 years of age; or,
 - surgically postmenopausal (bilateral oophorectomy or hysterectomy); or
 - sterile (surgically [bilateral tubal ligation] or the Essure Procedure). The Essure Procedure must have been inserted at least 3 months prior with documentation of the Essure confirmation test prior to Day 1 patch application. If the procedure was inserted less than 3 months prior to Day 1 patch application or proper documentation of the confirmation test was not provided, the volunteer agreed to use an additional non-hormonal medically acceptable method of birth control.

Exclusion Criteria

Volunteers or subjects who met any of the following criteria were excluded from the study:

1. Anyone who reported receiving any investigational drug within 28 days prior to Day 1 patch application.
2. Anyone who reported a clinically significant illness during the 28 days prior to Day 1 patch application as determined by the Investigator(s).
3. Anyone who reported a history of allergic response(s) to rivastigmine, other carbamate derivatives, or related drug.
4. Anyone who demonstrated a systolic blood pressure less than 90 mmHg or greater than 160 mmHg; a diastolic blood pressure less than 50 mmHg or greater than 95 mmHg; or a heart rate less than 50 beats per minute (bpm) or greater than 100 bpm, after a 5 minutes rest in a supine position at the Screening Visit.
5. Anyone who demonstrated a clinically relevant finding, as determined by the Investigator(s), on the screening ECG, such as second- or third-degree atrioventricular block or complete bundle branch block.
6. Anyone who reported a history of sick sinus syndrome, conduction defects (sinoatrial block, atrioventricular block), gastroduodenal ulcerative conditions, asthma or chronic obstructive pulmonary disease, urinary obstruction, or extrapyramidal symptoms such as tremor or seizures.
7. Anyone who reported a history or presence of clinically significant skin disorders (such as, but not limited to, psoriasis, vitiligo, or atopic dermatitis); difference of skin color amongst application sites; presence of excessive hair (subjects that agreed to have their hair clipped short [not shaved] prior to patch application were eligible),

- scar tissue, recent sunburn, tattoo, open sore, body piercing, or branding at the intended sites of application.
8. Anyone who reported a history of significant dermatologic cancers, for example, melanoma or squamous cell carcinoma. Basal cell carcinomas that were superficial and did not involve the investigative sites were acceptable.
 9. Anyone who reported a history of any medical conditions that may alter skin appearance, such as diabetes and porphyria.
 10. Anyone who reported a history of conditions that would significantly influence the immune response (e.g., primary or acquired immunodeficiencies such as HIV positive or AIDS, allergic diseases such as anaphylaxis, asthma or generalized drug reaction, neoplasms such as lymphoma or leukemia, rheumatoid arthritis, or systemic lupus erythematosus). At the discretion of the Investigator, minor allergic reactions to environmental allergens or foods, a remote history of asthma, and mild exercise-induced asthma need not be a reason for exclusion.
 11. Anyone who reported the use of any cholinergic, anticholinergic, or cholinomimetic compounds within 3 weeks prior to the initial patch application.
 12. Anyone who reported the use of any immunosuppressive drugs, as well as systemic and topical corticosteroids or retinoids within 28 days prior to Day 1 patch application.
 13. Anyone who reported the use of any medications or treatments that would significantly influence or exaggerate responses to the patches or that would alter inflammatory or immune responses to the patches within 21 days prior to Day 1 patch application (e.g., cyclosporine, tacrolimus, cytotoxic drugs, immune globulin, Bacillus Calmette- Guerin, monoclonal antibodies, radiation therapy).
 14. Anyone who reported the use of any anti-inflammatory medication, including ibuprofen and Celebrex, within 72 hours of Day 1 patch application, with the exception of steroid nose drops and/or eye drops.
 15. Anyone who reported the use of systemic or topical analgesics or antihistamines within 72 hours of Day 1 patch application. Aspirin (<650 mg/day) and acetaminophen were permitted.
 16. Anyone who reported a history of clinically significant allergies including food or drug allergies.
 17. Anyone who reported a history of sensitivity or allergy to adhesive bandages, tapes, or transdermal systems.
 18. Anyone who reported a significant history of allergy to soaps, lotions, emollients, ointments, creams, cosmetics, adhesives, or latex.
 19. Anyone who reported a history of drug or alcohol addiction or abuse within the past year.
 20. Females who were pregnant, lactating, breastfeeding, or intended to become pregnant over the course of the study.
 21. Females who demonstrated a positive pregnancy screen (females only).

Reviewer's Comment: *The inclusion and exclusion criteria are acceptable and consistent with the recommendations in the draft guidance.*

Procedures and Observations:

Tables 5 and 6 provide a summary of study events and procedures during the Induction and Challenge phases.

Table 5: Study Events and Procedures – Screening and Induction Phase

Activity		Induction Phase																					
Visit	Screen	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Study Day	-28 to 1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Obtain Consent	X	X																					
Inclusion/Exclusion	X	X																					
Medication History	X	X																					
Medical History	X	X																					
Pregnancy Test	X								X							X							X
Vital Signs	X																						
Safety 12-lead ECG	X																						
Product Application		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Product Removal			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess Adhesion			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Skin Reaction Evaluation			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Skin Reaction Evaluations were conducted 30 minutes ($\pm$ 10 minutes) after patch removal

Table 6: Study Events and Procedures – Rest Period and Challenge Phase

Activity	Rest Period	Challenge Phase				
Visit		23	24	25	26	27
Study Day	22-35	36	38	39	40	41
Pregnancy Test		X				X
Product Application		X				
Product Removal			X			
Assess Adhesion			X			
Skin Reaction Evaluation			X	X	X	X
Assess AEs		X	X	X	X	X
Concomitant Medication		X	X	X	X	X

Skin Reaction Evaluations were conducted 24, 48, 72 hours ($\pm$ 2 hours) after Day 38 patch removal (or if patch had detached, from the time of removal of the remaining patch).

Randomization:

Treatments were administered according to a randomization schedule prepared by Cetero. A randomization was generated independently from any clinic staff and was stored at each site. The generated randomization code determined which treatment (test or reference) was applied to the left upper arm and which treatment (test or reference) was applied to the right upper arm during the Induction Phase and which treatment (test or reference) was applied to the left side of the upper back and which treatment (test or reference) was applied to the right side of the upper back during the Challenge and Re-Challenge Phase for all subjects. All subjects received both treatments.

Subjects were assigned to their subject number and corresponding randomization in the order in which they entered the study. During the Irritation/Induction Phase, the patches were applied to the upper arms on Days 1 through 21. Sensitization application started on Day 36.

The same treatment sequence that was applicable during the Irritation/Induction Phase was applied during the Sensitization/Challenge Phase but to skin sites on the upper back. The patches applied for the sensitization evaluation were removed after 48 hours $\pm$ 4 hours by study staff other than the person who scored the sites.

Blinding:

Neither the dosing staff nor the subjects were blinded. However, the staff involved in monitoring the subjects, collecting subjective and objective data, and querying the subjects on adverse events (AEs) were blinded, as much as possible, to the product source under evaluation to maintain study integrity. The evaluator performed the assessments was blinded throughout the study.

Criteria for removal from the study:

The following were justifiable reasons for removing a subject from the study:

1. The subject experienced an AE following the administration of study medication that was intolerable as defined by the Investigator and/or the subject.
2. The subject was uncooperative or non-compliant.
3. In the Investigator's judgment, it was in the subject's best interest.
4. Consent was withdrawn.
5. Study termination by the Investigator or Sponsor.
6. A significant protocol violation, as defined by the Sponsor, occurred.

Any subject who showed irritation of such intensity that continued application of either 1 or more patches was deemed to be not medically appropriate, was discontinued from further applications. For safety reasons, subjects were monitored at frequent intervals until such time as the Investigator felt it was appropriate to discharge them from the study.

Any subject who had a patch detach and did not return to the clinical facility within 24 hours of the patch detachment for a replacement patch to be applied, was dropped from the study. Subjects who withdrew or were dropped from the study were not replaced.

Prior and Concomitant Medications:

Medications not excluded in the protocol may have been taken during the study. Once the study began, all medications used during the study were recorded.

No subjects used any cholinergic, anticholinergic, or cholinomimetic compounds for a period of 3 weeks prior to the first patch application and throughout the study. No subject used any immunosuppressive drugs, including systemic and topical corticosteroids and retinoids for a period of 28 days prior to Day 1 patch application and throughout the study. No subjects used any medications or treatments that would significantly influence or exaggerate responses to the patches or that would alter inflammatory or immune responses to the patches for a period of 21 days prior to Day 1 patch application and throughout the study (e.g., cyclosporine, tacrolimus, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin, monoclonal antibodies, radiation therapy). No subject used any anti-inflammatory medication, including ibuprofen and Celebrex (with the exception of steroid nose drops and/or eye drops) for a period of 72 hours prior to Day 1 patch application and throughout the

study. No subject used any systemic or topical analgesics or antihistamines for a period of 72 hours prior to Day 1 patch application and throughout the study. Aspirin (≤ 650 mg/day) and acetaminophen were permitted.

Reviewer's Comment: *It is not clear why aspirin was not considered as an anti-inflammatory drug and was permitted for use during the study. See comments later in this review under the Protocol Deviations section.*

The application sites and immediate surrounding area were not treated with any topical drugs, body lotions, make-up, creams, oils, or powders 48 hours before Day 1 patch application and throughout the study.

Female subjects that did not provide documentation of the Essure Procedure agreed to use a non-hormonal medically acceptable method of birth control throughout the study.

A contraceptive patch (e.g., Ortho Evra) must not have been used for at least 28 consecutive days prior to Day 1 patch application and throughout the end of the study to be eligible for study participation.

Female subjects of menopausal (peri- or post-) status were allowed to use hormone replacement therapy (HRT) with the exception of the following:

- Daily or weekly use of a patch HRT (e.g., Climara) must not have been used for at least 28 consecutive days prior to Day 1 patch application and through the end of the study.
- Over-the-counter topical HRT (e.g., cream, gel) must not have been used for at least 7 days prior to Day 1 patch application and through the end of the study. Prescription topical HRT (e.g., cream, gel) must not have been used for at least 14 days prior to Day 1 patch application and through the end of the study.

Compliance:

All study procedures were conducted on an outpatient basis. At each visit, subjects were queried regarding any AEs and concomitant medication usage since the last visit. These responses were recorded by the clinical staff.

Safety Measures

The Investigator or qualified medical designee was on-site for dosing and available by cell phone throughout the study. Supine (after 5 minutes rest) blood pressure, heart rate, respiratory rate and temperature were measured at screening. An ECG was recorded at screening.

Urine samples for pregnancy screen (females only) were collected at screening on Days 8, 15, 22, 36, and 41 (or early termination visit if a subject discontinued from the study prematurely). The staff recorded all AEs observed, queried, or spontaneously volunteered by the subjects. Irritation or sensitization scores up to a score of 3 were not considered AEs. However scores greater than 3, or if a patch or subject was dropped due to excessive irritation of the application site, were considered an AE. Subjects who experienced AEs

(including those withdrawn from the study due to an AE) were followed until the event(s) resolved to the satisfaction of the Investigator(s).

Any serious AE (SAE) was reported to the Sponsor within 24 – 48 hours of discovery. If the event was also unexpected, life-threatening, or fatal, the event was also reported to the IRB. Subjects withdrawn from the study due to any AEs were followed until an outcome was determined. All AEs, regardless of severity, were recorded in the appropriate section of the case report forms (CRFs).

2.4.3.1.2 Endpoints

Primary Endpoint

The primary endpoint of cumulative irritation score was the measurement of the combined “Dermal Response” and “Other Effect” total irritation scores recorded during the 21 day continuous application period (i.e., the total irritation score for a specific subject was the sum of the irritation scores recorded across all evaluations performed in the Irritation/Induction Phase).

Secondary Endpoint

There were no pre-specified secondary endpoints.

Irritation and Sensitization Evaluations:

Irritation response to the topical rivastigmine transdermal system was assessed approximately 30 minutes after patch removal during the Induction Phase on Days 2-22 by visual score using the following scoring scale:

Dermal responses:

- 0 = no evidence of irritation
- 1 = minimal erythema, barely perceptible
- 2 = definite erythema, readily visible; minimal edema or minimal papular response
- 3 = erythema and papules
- 4 = definite edema
- 5 = erythema, edema and papules
- 6 = vesicular eruption
- 7 = strong reaction spreading beyond application site

Other Effects (with corresponding numeric score):

- A (0) = slightly glazed appearance
- B (1) = marked glazed appearance
- C (2) = glazing with peeling and cracking
- F (3) = glazing with fissures
- G (3) = film of dried serous exudates covering all or part of the patch site
- H (3) = small petechial erosions and/or scabs

Sensitization response to the topical rivastigmine³ transdermal system was assessed at approximately 0.5, 24, 48 and 72 hours after patch removal on Day 38 by visual score using the same scoring scale.

Reviewer's Comment: *All patches during the study were secured by the tape. The draft guidance recommends assessing skin irritation associated with the tape separately from that of the patch. There were no separate analyses provided by the Sponsor for the taped area.*

Skin Adhesion Assessment:

Prior to patch removal on Days 2 through 22, a trained evaluator observed the patches and rated their degree of adhesion using the scoring system below. Only the adhesion of the patches was observed, the adhesion of the tape that had been applied over the patches was not scored. Adhesion was evaluated to ensure adequate skin contact for maximal induction of irritation and sensitization. Daily adhesion scores were tabulated with no statistical evaluation.

The adhesion score, a 5-point, ordinal, categorical variable with a scale corresponding to the amount of surface area exposed and ranges from 0 (10% or less) to 4 (100%) was used to measure adhesion in this study.

0 = 90% or more adhered (essentially no lift off of the skin)

1 = 75% to <90% adhered (some edges only lifting off of the skin)

2 = 50% to <75% adhered (less than half of the system lifting off of the skin)

3 = < 50% adhered but not detached (more than half the system lifting off of the skin but not detached)

4 = patch detached (patch completely off of the skin)

Reviewer's Comments: *The scales for irritation, sensitization, and patch adhesion are consistent with those recommended in the draft guidance. Since the patches were reinforced with the adhesion tape, data gathered on the adequacy of the adhesion in actual use is of limited value in this study.*

2.4.3.1.3 Statistical analysis plan

Analysis Population:

Subjects who receive all test patches and have made all required visits in both the Irritation/Induction Phase and the sensitization Challenge Phase without significant deviations were considered to have completed the study and were considered as being evaluable subjects for assessing the irritation and sensitization of the test and reference patches. The Analysis Populations were defined separately for each parameter and were defined per patch instead of per subject.

³ The sponsor's protocol erroneously stated estradiol instead of rivastigmine; this may have been a typo error.

Safety Population

All subjects who had at least one patch application were included in the Safety Population (SP). Any subject who had a patch detached and did not return to the clinical facility within 24 hours of the patch detachment, for a replacement patch to be applied, was dropped from the study but included in the SP.

Per-Protocol Population for Cumulative Irritation (PPPI)

The Per Protocol Population for Irritation (PPPI) consisted of all evaluable subjects who complete the 21 day Irritation/Induction Phase (without any period of detachment longer than 24 hours) and were included in the primary analysis of cumulative irritation. If a patch was moved or removed due to excessive irritation, the cumulative irritation score at that time was included using the Last Observation Carried Forward (LOCF) from the original discontinued application site. Discontinuation of any one patch did not preclude the continued dosing of the other patches unless continuation affected the safety of the subject as determined by the Investigator (or designee). Subjects who failed to complete the study for reasons other than excessive irritation (e.g., missed a visit, dropped for other safety reasons, non-compliance, etc.) were not included in the PPPI.

Per-Protocol Population for Sensitization (PPPS)

All evaluable subjects who complete the sensitization challenge, and had at least 1 post removal assessment completed at 48 or 72 hours following challenge patch removal were included in the PPPS.

Any subject who, after the patch was applied on Day 36, experienced a local reaction that required the patch to be removed prior to Day 38 was included in the PPPS, with the assessment at the time of removal considered their sensitization response with the observation carried forward for the 30 minute, 24, 48, and 72 hours scoring.

Any subject who removed a patch or had total patch detachment without immediate re-attachment for any other reason, prior to at least 44 hours of application, was not eligible for inclusion in the PPPS.

The PPPS for evaluation of sensitization was defined as follows:

A subject was considered potentially sensitized if all of the following criteria are met:

1. The subject had at least 1 evaluation occurring at 48 or 72 hours after the removal of the Challenge Phase patch.
2. The subject had a combined “Dermal Response” and “Other Effects” numeric score (e.g., cumulative irritation score) of at least 2 at their last evaluation during the Challenge Phase.
3. The combined “Dermal Response” and “Other Effects” numeric score (e.g., cumulative irritation score) obtained during the Challenge Phase evaluations were observed to be generally higher than the combined “Dermal Response” and “Other Effects” numeric scores obtained during the Induction Phase.
4. If the subject completed a Re-Challenge Phase, the above 3 criteria were met during both the Challenge Phase and the Re-Challenge Phase.

If a Re-Challenge was to be performed, all evaluable subjects who completed the sensitization Re-Challenge Phase, and had at least 1 post removal assessments completed at 48 or 72 hours following challenge patch removal were to be included in the Per Protocol Population for Re-Challenge Sensitization.

The primary endpoints of cumulative irritation and comparative sensitization used the PPPI and PPS respectively.

Any subject who showed irritation of such intensity that continued application of either 1 or more patches was not considered medically appropriate was discontinued from further applications and their irritation/other effects score at the time of discontinuation were carried forward (LOCF). They were included in the PPPI or PPS as appropriate with LOCF. Subject demographic and physical characteristic data were summarized for the Safety population using descriptive statistics (n, mean, median, standard deviation [SD], minimum, maximum).

Irritation Data and Analysis:

The primary analysis was a comparison of the overall mean of the observed total irritation score of the Test Patch against that of the Reference Patch. The PPPI was used for the primary analysis.

The primary objective related to irritation was whether the level of irritation of the Test Patch was inferior to that of the Reference Patch. Because the irritation measurement shows lower irritation for lower values, the relevant hypotheses for evaluating non-inferiority were:

H0: $\mu_T - (1.25 \times \mu_R) > 0$ (not non-inferior)

H1: $\mu_T - (1.25 \times \mu_R) \leq 0$ (non-inferior)

To demonstrate non-inferiority of the Test Product compared to the Reference Product, the upper bound of the one-sided 95% confidence interval (CI) of the mean cumulative irritation score for the test product (μ_T) minus 1.25 times the mean cumulative irritation score for the reference product (μ_R) must be less than or equal to 0. Other clinically relevant data, such as the number of applications that reached a maximal irritation score and the number of subjects that discontinued the product applications because of unacceptable irritation, were also evaluated. The same mean cumulative score could be reached with a small number of high scores (e.g., ≥ 3) as with a larger number of low scores (e.g., 1, which were of little clinical significance). Thus, it is difficult to determine the clinical meaningfulness of a given cumulative score or a given difference between products with regard to mean cumulative scores. Therefore, a meaningful degree of irritation (e.g., scores of ≥ 3) for each product. The proportion of subjects with a meaningful degree of irritation was to be no higher for the Test Product than for the Reference Product, and irritation should not have occurred earlier in the application period for the Test Product than for the Reference Product.

In the case where the mean total cumulative irritation scores for the test and reference treatments are both less than unity (1), which was the maximum difference between scores, the absolute difference between test and reference scores was also presented as a variable to evaluate non-inferiority of the test to the reference treatment. When most of the irritation

scores were 0, resulting in mean total cumulative irritation scores of <1, the analysis of relative differences between test and reference scores was inappropriate because small absolute differences in insignificantly low test and reference scores become more inflated on the relative scale than on the absolute scale compared to higher scores (e.g., parametric testing versus non-parametric testing).

Frequency tables showing the number of applications of each product with each dermal response score, other effects score, and cumulative irritation score (combined Dermal Response and Other Effect scores) on each study assessment day were created for the PPPI.

Tabulation, by patch type, of the number and percentage of subjects with each grade of irritation reaction on each study assessment day was provided. Frequency histograms were generated. Descriptive statistics (mean, SD, median, maximum, and minimum) of the irritation scores for each patch type for each assessment day was calculated and presented.

The irritation potential for each test article was determined by the scores obtained during the Induction Phase of the study. If at any evaluation during the Irritation/Induction Phase of the study, the scoring of irritation was 3 or greater on the irritation scale or significant “other effects” were observed, then continued application of that particular patch was carefully considered. If a score of 3 or greater was reached and the patch had to be moved to a new treatment site to continue the Induction Phase, the score of 3 was carried across the remainder of the assessment time points (as the LOCF) for purposes of determining the irritation potential for that particular Test or Reference Patch. Comparisons may have been constructed as appropriate to characterize the differences in irritation produced by the Test and Reference Patch.

Sensitization Data and Analysis:

If the scoring for irritation at either the 48 or 72 hour post Day 38 removal was greater than or equal to 2 on the irritation scale, or demonstrated a persistent and intense score judged by the Investigator to be suggestive of a sensitization reaction, then the subjects was considered to demonstrate a possible sensitization response to that specific patch type.

Subjects who demonstrate a potentially sensitizing response to either patch may have been Re- Challenged to both Test and Reference Patches at the request of the Sponsor. In such cases the patches were reapplied to naïve sites on the upper back of the identified subjects following the same procedures as defined for the original Challenge Phase.

The primary analysis of sensitization used the PPS, and compared the number and percentage of sensitization reactions (irritation score greater than or equal to 2 at 48 or 72 hours post removal) observed with each patch type.

Individual observations were presented by subject and by patch type. Tabulation by product of the number and percentage of subjects with each grade of irritation reaction was prepared for the 30 minute, 24, 48, and 72 hour evaluations after patch removal on Day 38.

If a reaction was observed that was more than the descriptive definition of the score recorded, a narrative description was to be provided, together with the opinion of the Investigator as to whether such reactions were felt to be indicative of a contact sensitization.

Frequency tables showing the number of applications of each product with each dermal response score, other effects score, and combined irritation score (Dermal Response and Other Effect scores) on each study assessment day were created for the PPPS.

For all subjects with at least 1 combined score of 2 or more at 48 or 72 hours after patch removal in the Challenge Phase, a table showing the actual scores for each subject at each evaluation time point during the Induction and Challenge Phases was completed. Scores that resolve before 48 hours were generally considered to be due to irritation instead of sensitization.

Descriptive statistics comparing the proportion of subjects sensitized or potentially sensitized to each test article was provided.

Adhesion Data:

Daily adhesion scores were tabulated with no statistical evaluation.

Reviewer's Comment: Since taping of the patches was allowed throughout the conduct of the study, adequacy of the adhesion in actual use cannot be assessed.

Safety Analysis:

All subjects who receive at least 1 patch application were included in the SP. Safety data obtained from reports of AEs was summarized by point of time of collection. Descriptive statistics (arithmetic mean, SD, median, minimum, and maximum) were calculated for quantitative safety data as well as for the difference from baseline (prior to the first patch application). Frequency counts were compiled for classification of qualitative safety data.

Irritation: During the Irritation/Induction Phase of the study, if at any evaluation the scoring of irritation was 3 or greater on the irritation scale or significant "other effects" were observed, then continued application of that particular patch to that site was carefully considered. The subject may have continued in the Induction portion of the study at the discretion of the Investigator for the specific and remaining patch. If the Investigator considered that based on the severity of irritation observed, further applications of a specific patch was inappropriate, that patch was discontinued.

All application site reactions were reported in data tables and in the detailed narrative description in the study report for each subject's response in both phases of this study. These included patient complaints such as dryness, itching, burning, pain, or soreness, etc., identifying to which application site the complaint applied. These reports were compared between Test Products. Adverse events were coded using the MedDRA dictionary and summarized for the number of subjects reporting the AE and the number of AEs reported. A by-subject AE data listing including verbatim term, coded term, and severity was provided.

No prospective calculations of statistical power were made.

Handling of Dropouts or Missing Data

Subjects who failed to complete the study for reasons other than excessive irritation (e.g., missed a visit, dropped for other safety reasons, non-compliance, etc.) were not included in the Per Protocol Population for Irritation.

Changes to Planned Analysis:

No changes in the planned conduct of the study or planned analyses occurred.

Reviewer's Comment: Study populations and statistical analysis plan are consistent with the draft guidance. This section of the protocol was also evaluated by the statistical team.

2.4.3.2 Study Conduct

Discussion of Patient Populations:

This multi-center study enrolled 280 subjects. One hundred forty subjects (Subjects (b) (6) (b) (6)) were enrolled at Cetero Research – Fargo, ND (Site 01) and 140 subjects (Subjects (b) (6) (b) (6)) were enrolled at Cetero Research – St. Charles, MO (Site 02). The study was conducted with 280 (230 completed) healthy adults.

Subjects started Day 1 of the Induction Phase by arriving at the clinic on 16 January 2012 at clinical sites 01 and 02 (Cetero Research – Fargo, ND and Cetero Research – St. Charles, MO). The subjects continued the study on an outpatient basis, returning for patch removal and application as well as irritation assessment during the Induction Phase and for patch application, removal and sensitization assessment during the Challenge Phase.

Table 7 presents the number of subjects who either began or completed each portion of the study. Two hundred and eighty healthy adult subjects were enrolled in the study and 229 subjects completed the clinical portion of the study in its entirety.

Table 7: Number of Subjects who Either Began or Completed Each Portion of the Study (The Sponsor's analysis)

Study Phase	Number of Subjects
Number of subjects who began the Induction Phase (Day 1)	280
Number of subjects included in the ITTI Population	280
Number of subjects who were discontinued during the Induction Phase [Between Day 1 (initial dose application) and 22 (prior to final assessments)]	35
Number of subjects who completed all dosing and assessments in the Induction Phase (Days 1-22)	245
Number of subjects included in the PPPI Population	262*
Number of subjects who were discontinued during the 14-day rest period [Between Day 22 (after skin and adhesion assessment) and Day 36 (prior to dosing)]	15
Number of subjects who began the Challenge Phase (Day 36)	230
Number of subjects included in the ITTS	230

Study Phase	Number of Subjects
Number of subjects who discontinued during the Challenge Phase [Between Day 36 (after dosing) and Day 41 (prior to final assessments)]	1
Number of subjects who completed the Challenge Phase (Day 36 – Day 41)	229
Number of subjects included in PPPS	229 for Test Product A and 228 for Reference Product B**
Number of subjects who were qualified as being potentially sensitized based on Challenge Phase results.	43

* Per the population definition in the protocol, subjects who were discontinued during the Induction Phase but had their LOCF carried forward were included in the PPPI ** One subject was excluded from the PPPS analysis for the Reference Product B only, due to insufficient Challenge Phase dose duration exposure.

The safety population included all subjects who received at least one patch application. Safety data from all 280 subjects were included in the safety population.

The Intent to Treat Irritation (ITTI) included all subjects who entered the cumulative irritation phase of the study and had at least 1 patch application. The ITTI included 280 of 280 subjects. The PPPI included all subjects who completed the 21 day Induction Phase of the study without any significant protocol deviations. Subjects who had any patch applications moved because of excessive irritation were included in the PPPI. Their last observations immediately prior to further patch applications being halted carried forward (LOCF) for the analysis. The PPPI included 262 of 280 subjects.

The Intent to Treat Sensitization (ITTS) for the Challenge Phase included all subjects who completed the cumulative Irritation Phase of the study and had patches applied for sensitization analysis during the Challenge Phase. Any subject who removed a patch for any other reason prior to at least 44 hours of application was included in the ITTS. The ITTS included 230 of the 280 subjects in the Challenge Phase.

The PPPS for the Challenge Phase included all subjects who completed the Induction Phase, had patches applied for sensitization analysis during the Challenge Phase, and had at least one post-removal assessment completed at 48 or 72 hours of patch removal. There were 230 subjects in the Challenge Phase. The PPPS for the Challenge Phase included 229 of 230 subjects for Test Product A and 228 of 230 subjects for Reference Product B.

Reviewer's Comment: *The number of subjects completing the study is adequate. The draft guidance recommends at least 200 evaluable subjects, this study had a total of 229 completers.*

A total of 48 subjects discontinued the study prematurely for the following reasons:

- *Application site reaction – 26*
- *Adverse events – 3*
- *Pregnancy – 1*
- *Protocol violations – 3*
- *Noncompliance with the study procedures or for personal reasons – 15*

The Sponsor's justifications for the excluded subjects seems to be reasonable. Fifteen subjects discontinued from the study due to excessive irritation were excluded from the PPS only; however, they were included in the PPPI with their LOCF. This is acceptable.

Protocol Deviations

Table 8: List of Protocol Deviations (The Sponsor's analysis)

Type	Subject No.
Day 1 dosing error, subject was dosed with 2 "B" patches instead of 1 "A" patch and 1 "B" patch; subject was dropped from the study	(b) (6)
Day 2 patches not applied within 24 hours $\pm$ 1 hour (patches were applied between 21 hours 59 minutes and 22 hours 58 minutes)	
Day 2 irritation evaluation not completed within 30 minutes $\pm$ 10 minutes of patch removal (irritation evaluation was completed within 41 minutes)	
Day 3 adhesion evaluation of right arm patch not collected	
Day 3 patches not applied within 24 hours $\pm$ 1 hour (patches were applied between 22 hours 49 minutes and 22 hours 52 minutes)	
Day 3 patches not applied within 24 hours $\pm$ 1 hour (patches were applied between 25 hours 5 minute and 25 hours 6 minutes)	
Day 4 patches not applied within 24 hours $\pm$ 1 hour (patches were applied within 25 hours 2 minutes)	
Day 5 patches not applied within 24 hours $\pm$ 1 hour (patches were applied within 22 hours 46 minutes)	
Day 5 patches not applied within 24 hours $\pm$ 1 hour (patches were applied between 25 hours 2 minutes and 25 hours 14 minutes)	
Day 6 patches not applied within 24 hours $\pm$ 1 hour (patches were applied between 22 hours 29 minutes and 22 hours 58 minutes)	
Day 6 patches not applied within 24 hours $\pm$ 1 hour (patches were applied between 25 hours 7 minutes and 25 hours 27 minutes)	
Day 7 subject used a restricted concomitant medication (topical analgesics) and was dropped from the study	
Day 7 patches not applied within 24 hours $\pm$ 1 hour (patches were applied between 22 hours 33 minutes to 22 hours 58 minutes)	

Type	Subject No.
Day 7 irritation evaluation not completed within 30 minutes $\pm$ 10 minutes of patch removal (irritation evaluation was completed within 45 minutes)	(b) (6)
Day 8 adhesion evaluation of right arm patch not collected	
Day 8 patches not applied within 24 hours $\pm$ 1 hour (patches were applied between 25 hours 1 minute and 25 hours 5 minutes)	
Day 9 patches not applied within 24 hours $\pm$ 1 hour (patches were applied between 25 hours 2 minutes and 25 hours 4 minutes)	
Day 10 patches not applied within 24 hours $\pm$ 1 hour (patches were applied between 22 hours 48 minutes and 22 hours 58 minutes)	
Day 11 patches not applied within 24 hours $\pm$ 1 hour (patches were applied within 25 hours 8 minutes)	
Day 13 patches not applied within 24 hours $\pm$ 1 hour (patches were applied within 22 hours 51 minutes)	

Type	Subject No.
Day 14 patches not applied within 24 hours ± 1 hour (patches were applied between 25 hours 1 minute and 25 hours 9 minutes)	(b) (6)
Day 15 irritation evaluation not completed within 30 minutes ± 10 minutes of patch removal (irritation evaluation was completed 4 minutes after patch removal)	
Day 15 patches not applied within 24 hours ± 1 hour (patches were applied between 25 hours 12 minutes and 25 hours 18 minutes)	
Day 16 patches not applied within 24 hours ± 1 hour (patches were applied within 22 hours 28 minutes)	
Day 19 patches not applied within 24 hours ± 1 hour (patches were applied between 25 hours 3 minutes and 25 hours 35 minutes)	
Day 20 patches not applied within 24 hours ± 1 hour (patches were applied between 22 hours 54 minutes and 22 hours 58 minutes)	
Day 21 patches not applied within 24 hours ± 1 hour (patches were applied between 25 hours 5 minutes and 25 hours 7 minutes)	
Day 21 dosing error, subject was dosed with 2 “B” patches instead of 1 “A” patch and 1 “B” patch; subject was dropped from the study	
Day 22 AE query not completed	
Day 22 irritation evaluation not completed within 30 minutes ± 10 minutes of patch removal (irritation evaluation was completed 0 minutes after patch removal)	
Day 36 left site patch not worn for 48 hours ± 4 hours (left site patch was worn for 25 hours 58 minutes); subject was excluded from the PPS for that patch	

Reviewer’s Comment: *According to the protocol, subjects were not supposed to take any anti-inflammatory medication except for aspirin or acetaminophen. Two subjects in the study were taking aspirin on a daily basis, one (subject (b) (6)) was on 81 mg, the other one (subject (b) (6)) on 325 mg dose. Only one subject used acetaminophen 500 mg once.*

The Sponsor states that no subjects used any anti-inflammatory medication. However, there was one subject (subject (b) (6)) who took 200 mg ibuprofen for backache. Ibuprofen is anti-inflammatory drug and could potentially suppress the inflammation caused by the patches. However, since this subject took only one dose over a 36 day trial, it is acceptable to keep this subject in the PPPI.

Other protocol deviations do not seem to have had a major impact on the overall outcome of the study results. All of the subjects listed in Table 8 should be included in the PPPI.

Retention of Reserve Samples:

The Investigator was responsible for dispensing and accounting for all investigational products, and exercising accepted medical and pharmaceutical practices. Records were kept of all drugs received from and returned to the Sponsor. At the end of the study, all study drug was accounted for; any unused drug was inventoried and retained on site as retention samples.

Demographics:

Two hundred eighty healthy non-smoking subjects (76 males and 204 females) were enrolled in the study. Tables 9 summarizes demographic data for the test and reference products.

Table 9: Summary of Demographic Data for ITTI Population (The Sponsor’s analysis)

		All Subjects N=280
Age	Mean Range	39.6 18 – 65
Sex	Male Female	76 (27.1%) 204 (72.9%)
Race	American Indian or Alaskan Native	3 (1.1%)
	Asian	2 (0.7%)
	Black or African American	50 (17.9%)
	White/Not-Hispanic	222 (79.3%)
	White and Asian	1 (0.4%)
	White and American Indian or Alaskan Native	2 (0.7%)

***Reviewer’s Comment:** The study population was predominantly white, with 2/3 female; none of the subjects were outside the age limits of 18-65 recommended by the draft guidance. The guidance does not specify required demographics of the study population, it only recommends the study be conducted in multiple centers with different climate conditions. This study was conducted in two sites (Fargo, ND and St. Charles, MO) enrolling 140 subjects at each site.*

2.4.3.3 Results

Irritation:

To demonstrate non-inferiority of the Test Product compared to the Reference Product with regard to the cumulative irritation scores, the scores for the Reference Product were scaled by multiplying individual total cumulative irritation scores by 1.25.

To demonstrate non-inferiority of the Test Product compared to the Reference Product with regard to the cumulative irritation scores, the upper bound of the one-sided 95% CI of the mean cumulative irritation score for Test Product minus the mean scaled cumulative irritation score for Reference Product must be less than or equal to zero. Table 10 summarizes the results for general linear methodology for the PPPI.

Table 10: Statistical Results of Induction Phase Irritation Analysis (PPPI Population) (N=262) (The Sponsor’s analysis)

Variable	Hypotheses	A-1.25B	Upper Bound of One-Sided 95% Confidence Limit
Cumulative Irritation Scores (Dermal Response + Other Effect Scores) (Test – 1.25*Reference)	H ₀ : $\mu_T - 1.25 \mu_R > 0$ H ₁ : $\mu_T - 1.25 \mu_R \leq 0$	-8.60592	-7.82006

*A = Test Product, B = Reference Product

The upper bound for the 95% confidence interval was less than zero, which indicated that the Test Product is non-inferior to the Reference Product.

Frequency of the combined local irritation scores for the test and the reference product are presented in tables 11 and 12, respectively.

Table 11: Frequency of Combined Local Reaction Scores* for the Test Patch (PPPI) (The Sponsor's analysis)**

Score	Day 4	Day 7	Day 10	Day 13	Day 15	Day 17	Day 20	Day 22	Total
0	104 (39.69%)	67 (25.87%)	37 (14.34%)	17 (6.61%)	16 (6.23%)	7 (2.72%)	8 (3.19%)	8 (3.23%)	946 (17.53%)
1	128 (48.85%)	112 (43.24%)	96 (37.21%)	85 (33.07%)	87 (33.85%)	84 (32.68%)	82 (32.67%)	85 (34.27%)	2033 (37.68%)
2	22 (8.40%)	69 (26.64%)	116 (44.96%)	136 (52.92%)	131 (50.97%)	135 (52.53%)	129 (51.39%)	131 (52.82%)	2045 (37.90%)
3	0 (0.00%)	3 (1.16%)	0 (0.00%)	1 (0.39%)	2 (0.78%)	2 (0.78%)	5 (1.99%)	6 (2.42%)	48 (0.89%)
4	3 (1.15%)	2 (0.77%)	1 (0.39%)	8 (3.11%)	6 (2.33%)	12 (4.67%)	11 (4.38%)	5 (2.02%)	120 (2.22%)
5	3 (1.15%)	1 (0.39%)	6 (2.33%)	7 (2.72%)	10 (3.89%)	13 (5.06%)	10 (3.98%)	6 (2.42%)	128 (2.37%)
6	1 (0.38%)	2 (0.77%)	2 (0.78%)	3 (1.17%)	5 (1.95%)	4 (1.56%)	3 (1.20%)	4 (1.61%)	51 (0.95%)
7	1 (0.38%)	3 (1.16%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.80%)	3 (1.21%)	20 (0.37%)
8	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
9	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.40%)	0 (0.00%)	4 (0.07%)

* Combined local reaction scores = irritation + other effects. ** Data derived from the Sponsor's table 1.5a (Appendix 16.1.9).

Table 12: Frequency of Combined Local Reaction Scores* for the RLD Exelon Patch (PPPI) (The Sponsor's analysis)**

Score	Day 4	Day 7	Day 10	Day 13	Day 15	Day 17	Day 20	Day 22	Total
0	104 (39.69%)	51 (19.69%)	24 (9.30%)	5 (1.95%)	15 (5.84%)	11 (4.28%)	8 (3.19%)	7 (2.82%)	787 (14.58%)
1	123 (46.95%)	112 (43.24%)	106 (41.09%)	90 (35.02%)	82 (31.91%)	85 (33.07%)	87 (34.66%)	88 (35.48%)	2123 (39.34%)
2	24 (9.16%)	87 (33.59%)	123 (47.67%)	145 (56.42%)	141 (54.86%)	136 (52.92%)	135 (53.78%)	129 (52.02%)	2195 (40.68%)
3	2 (0.76%)	2 (0.77%)	0 (0.00%)	3 (1.17%)	1 (0.39%)	0 (0.00%)	2 (0.80%)	3 (1.21%)	31 (0.57%)
4	4 (1.53%)	1 (0.39%)	2 (0.78%)	9 (3.50%)	9 (3.50%)	11 (4.28%)	9 (3.59%)	9 (3.63%)	119 (2.21%)
5	4 (1.53%)	3 (1.16%)	3 (1.16%)	3 (1.17%)	5 (1.95%)	9 (3.50%)	4 (1.59%)	4 (1.61%)	82 (1.52%)
6	0 (0.00%)	1 (0.39%)	0 (0.00%)	2 (0.78%)	4 (1.56%)	4 (1.56%)	3 (1.20%)	4 (1.61%)	36 (0.67%)
7	1 (0.38%)	2 (0.77%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.39%)	2 (0.80%)	3 (1.21%)	17 (0.32%)
8	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
9	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.40%)	1 (0.40%)	5 (0.09%)

*Combined local reaction scores = irritation + other effects. ** Data derived from the Sponsor's table 1.5b (Appendix 16.1.9).

Table 13: Number of Subjects with Patch Moved and Number of Patches Moved During Induction Phase of the Study (PPPI) (The Sponsor's analysis)

	Number of Subjects	Number of Patches
	N (%)	N
Test Product: Rivastigmine Patch (Transdermal System) 4.6 mg/24 hours	58 (22.14%)	90
Reference Product: EXELON Patch (Rivastigmine Transdermal System) 4.6	53 (20.23%)	84

No patches were moved due to unacceptable degree of irritation in the Challenge phase of the study.

Table 14: Comparison of the Cumulative Irritation Scores between the Test and the Reference Products for Day 22 and Total with LOCF (PPPI)*

Score	Test Product A		Reference Product B	
	Day 22	Total	Day 22	Total
0	6 (2.29%)	934 (16.98%)	6 (2.29%)	779 (14.16%)
1	75 (28.63%)	2001 (36.37%)	76 (29.01%)	2063 (37.50%)
2	119 (45.42%)	1967 (35.75%)	124 (47.33%)	2118 (38.50%)
3	18 (6.87%)	127 (2.31%)	12 (4.58%)	100 (1.82%)
4	32 (12.21%)	342 (6.22%)	34 (12.98%)	325 (5.91%)
5	9 (3.44%)	81 (1.47%)	8 (3.05%)	86 (1.56%)
6	3 (1.15%)	50 (0.91%)	2 (0.76%)	31 (0.56%)

* Data derived from the sponsor's Table 1.6a and Table 1.6b (Appendix 16.1.9)

Table 15 shows the summary of the descriptive statistics of the cumulative irritation scores for each treatment for the PPPI.

Table 15: Summary of Descriptive Statistics for Cumulative Combined Irritation Scores for Test Product and Reference Product Using LOCF (The Sponsor's analysis)

Cumulative Irritation Scores (Dermal Response + Other Effects)	Test Product A: Rivastigmine Transdermal System,	Reference Product B: Exelon Patch (Rivastigmine Transdermal System) 4.6 mg/24 hours
N	262	262
Mean	32.02	32.50
Median	34	35
Standard Deviation	18.57	17.64
Max	121	121
Min	2	2

Table 16: Summary of Induction Phase Scores and Frequencies using LOCF for Test Product A from Day 13 to Day 22 (PPPI=262) (The Sponsor's Analysis)

Score	Day 13 N (%)	Day 14 N (%)	Day 15 N (%)	Day 16 N (%)	Day 17 N (%)	Day 18 N (%)	Day 19 N (%)	Day 20 N (%)	Day 21 N (%)	Day 22 N (%)
0	17 (6.49%)	30 (11.45%)	16 (6.11%)	14 (5.34%)	6 (2.29%)	13 (4.96%)	8 (3.05%)	5 (1.91%)	5 (1.91%)	6 (2.29%)
1	84 (32.06%)	75 (28.63%)	85 (32.44%)	81 (30.92%)	83 (31.68%)	77 (29.39%)	77 (29.39%)	78 (29.77%)	75 (28.63%)	75 (28.63%)
2	132 (50.38%)	124 (47.33%)	125 (47.71%)	125 (47.71%)	127 (48.47%)	122 (46.56%)	124 (47.33%)	123 (46.95%)	124 (47.33%)	119 (45.42%)
3	5 (1.91%)	5 (1.91%)	6 (2.29%)	7 (2.67%)	8 (3.05%)	12 (4.58%)	12 (4.58%)	14 (5.34%)	14 (5.34%)	18 (6.87%)
4	17 (6.49%)	21 (8.02%)	21 (8.02%)	24 (9.16%)	26 (9.92%)	26 (9.92%)	29 (11.07%)	30 (11.45%)	32 (12.21%)	32 (12.21%)
5	4 (1.53%)	4 (1.53%)	6 (2.29%)	8 (3.05%)	9 (3.44%)	9 (3.44%)	9 (3.44%)	9 (3.44%)	9 (3.44%)	9 (3.44%)
6	3 (1.15%)	3 (1.15%)	3 (1.15%)	3 (1.15%)	3 (1.15%)	3 (1.15%)	3 (1.15%)	3 (1.15%)	3 (1.15%)	3 (1.15%)

Note: Results are based on the scores of original sites.

Table 17: Summary of Induction Phase Scores and Frequencies using LOCF for Reference Product B from Day 13 to Day 22 (PPPI=262) (The Sponsor’s Analysis)

Score	Day 13 N (%)	Day 14 N (%)	Day 15 N (%)	Day 16 N (%)	Day 17 N (%)	Day 18 N (%)	Day 19 N (%)	Day 20 N (%)	Day 21 N (%)	Day 22 N (%)
0	5 (1.91%)	12 (4.58%)	15 (5.73%)	8 (3.05%)	10 (3.82%)	9 (3.44%)	3 (1.15%)	6 (2.29%)	3 (1.15%)	6 (2.29%)
1	88 (33.59%)	93 (35.50%)	80 (30.53%)	87 (33.21%)	82 (31.30%)	84 (32.06%)	84 (32.06%)	79 (30.15%)	76 (29.01%)	76 (29.01%)
2	142 (54.20%)	129 (49.24%)	135 (51.53%)	130 (49.62%)	130 (49.62%)	126 (48.09%)	125 (47.71%)	127 (48.47%)	130 (49.62%)	124 (47.33%)
3	6 (2.29%)	6 (2.29%)	7 (2.67%)	7 (2.67%)	7 (2.67%)	8 (3.05%)	9 (3.44%)	9 (3.44%)	9 (3.44%)	12 (4.58%)
4	15 (5.73%)	16 (6.11%)	17 (6.49%)	20 (7.63%)	23 (8.78%)	25 (9.54%)	31 (11.83%)	31 (11.83%)	34 (12.98%)	34 (12.98%)
5	4 (1.53%)	4 (1.53%)	6 (2.29%)	8 (3.05%)	8 (3.05%)	8 (3.05%)	8 (3.05%)	8 (3.05%)	8 (3.05%)	8 (3.05%)
6	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)

Note: Results are based on the scores of original sites.

Reviewer’s Comment: Summary tables 11-14 above provide scores only for the selective days of the study. These data were derived from the sponsor’s summary tables. Overall, data showed similar trends in frequency and severity of irritation scores for the test and the RLD patches.

The majority of the study subjects developed irritation to the tested patches over the 21-day induction phase. By Day 22, 256 (97.7%) out of 262 subjects in both treatment arms had at least a score of 1 for irritation, almost half of the study population developed a score of 2 (45.2% for the Test Product A and 47.7% for the Reference Product B). There was no difference between the treatment arms in the percentages of subjects developing irritation by scores of severity. The means of cumulative irritation scores were similar in both treatment arms (32.02±18.57 for the Test Product A vs. 32.5±17.64 for the Reference Product B).

The number of subjects that required the patch to be moved due to irritation was similar in both treatment groups. The number of subjects discontinuing the study due to local irritation was relatively low (N=26); none of those discontinuations were due to excessive irritation in the Challenge phase.

There was one skin irritation and sensitization study (Study #W160) in healthy subjects conducted with the RLD Exelon® patch during its development program⁴. This study was of similar design with a 21-day Induction phase, followed by Challenge and Re-Challenge; however, scoring system was different (the lowest “positive” score rating was 0.5, not 1). One dose strength, 9.5 mg/24 hours, was tested in the study. A total of 138 subjects were enrolled; 117 completed the Induction and Challenge phases.

Overall, at 24 hours after the first patch was removed, 27% of subjects showed a reaction of 0.5 or above, 18.1% had a skin irritation score of 2 or above. Only six subjects showed a skin irritation score of 3, i.e. erythema with induration and vesicles, during the study. The highest incidence of skin irritation was observed after the 8th patch was removed with 56% of subjects showing some irritation. In the challenge period, 68% of subjects showed faint

⁴ Data source: EDR - the original NDA 022083 submission (dated 9/8/2006), Clinical section, final study reports.

or slight erythema immediately after the patch was removed, with 15% of subjects showing at least intense erythema.

It seems that the overall incidence of irritation during the RLD development was lower. For example, the incidence of irritation after the first patch was 27 % in Study W160 compared to 41% and 44% for the generic and Exelon® patches in Study C10-1870; the incidence of erythema after the 8th patch application in the study W160 was 56% compared to 77% for the generic and 84 % for the RLD in Study C10-1870. However, it is difficult to do comparisons across the studies. Cumulative irritation scores were not provided in the W160 study report. It is not known if the formulation of the Exelon patch used in Study W160 is the same as currently approved and used in Study C10-1870.

The FDA statistician’s analyses confirmed the Sponsor’s results for irritation. Their analyses for irritation are summarized below.

Statisticians were asked to conduct an analysis of the combined scores (dermal response + numeric score of other effects) by day of assessment and total with LOCF for the PPPI. They were also asked to exclude the following subjects from the PPPI: (b) (6) (as per the Sponsor’s exclusions) and additional two subjects (b) (6). Therefore, the final sample size for the PPPI in the FDA’s analyses was 260.

Table 18: Summary of Descriptive Statistics for Cumulative Combined Irritation Scores for Test Product and Reference Product Using LOCF - FDA Statistical Review

Cumulative Irritation Scores (Dermal Response + Other Effects)	Test Product: Rivastigmine Transdermal System, 4.6 mg/24 hours	Reference Product: Exelon Patch (Rivastigmine Transdermal System) 4.6 mg/24 hours
N	260	260
Mean (Standard Deviation)	32.1(18.6)	32.6(17.7)
Median	33.5	35
Max	121	121
Min	2	2

The following Table 19 presents the frequency of irritation scores for each test article on each study day.

Table 19: Frequency of irritation scores using LOCF (PPPI, N=260) – FDA Statistical Review

Visit Day	Treatment	Scores						
		0	1	2	3	4	5	6
Day 8	Test	59	144	72	3	9	1	2
	Reference	43	112	92	2	8	2	1
Day 15	Test	16	84	124	6	21	6	3
	Reference	15	79	134	7	17	6	2

Visit Day	Treatment	Scores						
		0	1	2	3	4	5	6
Day 22	Test	6	74	118	18	32	9	3
	Reference	6	75	123	12	34	8	2

Table 20: Analysis for the mean cumulative irritation scores using mixed model (PPPI) (N=260) – FDA Statistical Review

Test (Mean μ_T)	Reference (Mean μ_R)	$\mu_T - 1.25\mu_R$	Upper limit one-sided 95% CB ($\mu_T - 1.25\mu_R$)	Pass the Non-inferiority test
1.5237	1.5502	-0.4104	-0.3728	Yes

Non-inferiority analyses based on the mean cumulative irritation scores (primary endpoint) showed that the 95% UCL for the adjusted mean difference ($\mu_T - 1.25\mu_R$) was less than zero. Therefore, the irritation potential of the test patch is no worse than that of the reference patch.

Sensitization:

The PPPS for the Challenge Phase included all subjects who completed the Induction Phase, had patches applied for sensitization analysis during the Challenge Phase, and had at least one post-removal assessment completed at 48 or 72 hours of patch removal. There were 230 subjects in the Challenge Phase. The PPPS for the Challenge Phase included 229 of 230 subjects for Test Product A and 228 of 230 subjects for Reference Product B.

Forty-three subjects (43/228 or 18.9%) in the PPPS demonstrated a possible sensitization reaction to both transdermal systems in the Challenge Phase. Of the 43 subjects, no subject demonstrated a possible sensitization reaction for only the Test Product or only the Reference Product. As the propensity for causing sensitization for Test Product A and Reference Product B was the same, a Re-Challenge was not conducted to confirm sensitization.

Tables 21 through 24 below provide the Sponsor’s summary of results on sensitization.

Table 21: Summary of Challenge Phase Irritation Evaluation Scores and Frequencies for Test Product A During the Challenge Phase (PPPS – N=229) (The Sponsor’s analysis)

Combined Irritation Score	Time Point After Dose-Removal			
	30 minute	24 hour	48 hour	72 hour
	N (%)	N (%)	N (%)	N (%)
0	58 (25.33%)	82 (35.81%)	114 (49.78%)	169 (73.80%)
1	69 (30.13%)	86 (37.55%)	75 (32.75%)	30 (13.10%)
2	100 (43.67%)	59 (25.76%)	37 (16.16%)	24 (10.48%)
3	2 (0.87%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
4	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (1.31%)
5	0 (0.00%)	2 (0.87%)	3 (1.31%)	3 (1.31%)

Table 22: Summary of Challenge Phase Irritation Evaluation Scores and Frequencies for Reference Product During the Challenge Phase (PPPS – N=228) (The Sponsor’s analysis)

Combined Irritation Score	Time Point After Dose-Removal			
	30 minute	24 hour	48 hour	72 hour
	N (%)	N (%)	N (%)	N (%)
0	52 (22.81%)	81 (35.53%)	111 (48.68%)	171 (75.00%)
1	72 (31.58%)	88 (38.60%)	77 (33.77%)	27 (11.84%)
2	102 (44.74%)	58 (25.44%)	36 (15.79%)	24 (10.53%)
3	2 (0.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
4	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (1.32%)
5	0 (0.00%)	1 (0.44%)	4 (1.75%)	3 (1.32%)

Table 23: Descriptive Statistics of Combined Irritation Scores for Test Product During the Challenge Phase (PPPS – N=229) (The Sponsor’s analysis)

Descriptive Statistics	30 min	24 hour	48 hour	72 hour
N	229	229	229	229
Mean	1.20	0.93	0.72	0.46
Standard Deviation	0.83	0.87	0.89	0.94
Median	1	1	1	0
Min	0	0	0	0
Max	3	5	5	5

Table 24: Descriptive Statistics of Combined Irritation Scores for Reference Product

During the Challenge Phase (PPPS – N=228) (The Sponsor’s analysis)

Descriptive Statistics	30 min	24 hour	48 hour	72 hour
N	228	228	228	228
Mean	1.24	0.92	0.74	0.45
Standard Deviation	0.81	0.82	0.93	0.94
Median	1	1	1	0
Min	0	0	0	0
Max	3	5	5	5

Reviewer’s Comments: The proportion of subjects positive to sensitization was similar in both treatment groups. Most of those who developed irritation to the patches in the Challenge phase had a score of 1 or 2. Only three subjects (b) (6) in the test product A arm and four subjects (b) (6) in the reference product B arm developed irritation scores of 4-5. The draft guidance on rivastigmine recommends a re-challenge test four to eight weeks following the original challenge for all subjects with a potential sensitization reaction. Forty-three subjects (43/228 or 18.9%) in the PPPS demonstrated a possible sensitization reaction to both transdermal systems in the Challenge Phase. The study protocol states that subjects who demonstrate a potentially sensitizing response to either patch may be re-challenged to both test and reference patches at the request of the study Sponsor. The Sponsor chose not to do this based on the fact that none of the subjects developed sensitization to only one of the tested patches. This is acceptable.

FDA Statistical Review confirmed the sponsor’s results for sensitization. Table 25 presents the 95% UCL for the difference in proportions of potentially sensitized patients for the test versus reference, using the Sensitization Per-Protocol population (PPPS). Based on the 95% UCL for the difference in proportions, the test might exceed the reference by at most 1.3 percentage points with regard to the proportion of subjects who had sensitization.

Table 25: McNemar confidence bound based on the numbers of subjects with potentially sensitized scores – FDA Statistical Review

Test patch potentially sensitized and reference patch not potentially sensitized (P _T)	Test patch not potentially sensitized and reference patch potentially sensitized (P _R)	Total N	P _T -P _R	One-sided 95% Upper Bound *	
				McNemar	Clopper
0	0	228	0	0.0044	0.0131

*: One-sided 95% CB for P_T-P_R, where P_T=P(potentially sensitized for test product), and P_R=P(potentially sensitized for reference product)

The statistical reviewer concluded that the irritation and sensitization potential of the test product is not worse than that of the RLD Exelon® patch.

Adhesion:

Four subjects (b) (6) reportedly had a score of “1” for adhesion (i.e., 75-90% adhered). Two subjects (b) (6) had a complete detachment of the patch. Both of these subjects had moderate irritation at the site of the patch application. Subject (b) (6) was

discontinued from the study after Day 22 due to excessive irritation, Subject (b) (6) completed the study.

Reviewer's Comment: This study was not designed to assess the adequacy of adhesion of the patch; hypoallergenic tape was applied to secure the patches in place. See review of the study R10-1307 for the adhesion assessment.

2.4.4 Detailed Review of Patch Adhesion Study (Study R10-1307)

2.4.4.1 Protocol

Sponsor's protocol#:	R10-1307
Title	A Study to Evaluate the Relative Bioavailability and Adhesive Properties of Rivastigmine 9.5 mg/24 hours Patch (Transdermal System) versus Exelon 9.5 mg/24 hours Patch (Transdermal System) in Normal Healthy Volunteers
Objectives	To assess the relative bioavailability and adhesion of Rivastigmine 9.5 mg/24 hours Patch (Transdermal System) compared to that of Exelon 9.5 mg/24 hours Patch (Rivastigmine Transdermal System) following a 24-hour application period in healthy adult subjects

2.4.4.1.1 Study Design

Randomized, single-dose, 2-period, 2-treatment, open-label crossover bioavailability and adhesion study conducted under fasting conditions.

This was a randomized, single-dose, 2-period, 2-treatment, open-label crossover bioavailability and adhesion study conducted under fasting conditions. A total of 30 healthy adult subjects (male and female) were enrolled in the study. The total duration of the study, screening through study exit, was approximately 7 weeks with a 7-day washout period between doses. At study check-in for each period, the subjects reported to the clinical site at least 10 hours prior to Day 1 patch application and were required to stay for 36 hours after Day 1 patch application. On Day 1 (Period I) and Day 8 (Period II), each subject received either a single patch application of the test product, Rivastigmine Transdermal System, 9.5 mg/24 hours, or a single patch application of the reference product, Exelon Patch, 9.5 mg/24 hours, to the upper back following an overnight fast of at least 10 hours. The patches were worn for a period of 24 hours. Taping or any external reinforcement of the patches was not allowed throughout the conduct of the study. Following the washout period, subjects returned to the clinical facility to be dosed with the alternative treatment to the opposite side of the upper back as per the randomization. Blood samples were collected within 90 minutes prior to dosing (0 hour) and after dose administration at 0.5, 1, 2, 4, 6, 8, 9, 10, 11, 12, 13, 14, 16, 18, 20, 22, 24 (prior to patch removal), 26, 28, 30, 32, and 36 hours while subjects were confined to the clinic. The actual time of sample collection was documented. Patch

adhesion was evaluated at 0 (immediately following patch application), 2, 4, 6, 8, 10, 12, 18, and 24 hours ($\pm$ 10 minutes) after patch application.

Reviewer's Comment: *The study design for assessment of patch adhesion is acceptable.*

Treatments:

Treatments

Treatment consisted of the following:

Treatment	Description
Test (A)	Rivastigmine Transdermal System, 9.5 mg/24 hours
Reference (B)	Exelon® Patch, 9.5 mg/24 hours

* Patch manufactured by (b) (4) (Lot No. C0004AL0AU); **Patch manufactured by LTS Lohmann Therapy Systems Corp.

Study Population:

Inclusion Criteria

Volunteers who met the following criteria were included as subjects in the study.

1. Informed of the nature of the study, agreed to, and were able to read, review, and sign the informed consent document prior to Period I patch application. The informed consent document was written in English, therefore the volunteer must have had the ability to read and communicate in English.
2. Completed the screening process within 28 days prior to Period I patch application.
3. Healthy male or female, 18 – 65 years of age, inclusive, at the time of Period I patch application.
4. Body mass index (BMI) between 18 kg/m² – 32 kg/m², inclusive, and weighed at least 110 lbs.
5. Judged by an Investigator to be in good health as documented by medical history, physical examination (including but not limited to an evaluation of the cardiovascular, gastrointestinal, respiratory, and central nervous systems), vital sign assessments, 12-lead electrocardiogram (ECG), clinical laboratory assessments, and by general observations. Any abnormalities or deviations outside the normal ranges for any clinical testing (laboratory tests, ECG, vital signs) could be repeated at the discretion of the Investigator(s) and judged to be not clinically significant (NCS) for study participation.
6. Females were:
 - a. of childbearing potential and practicing an acceptable method of birth control as judged by the Investigator(s); or,
 - b. naturally postmenopausal (no menses) for at least 1 year and if < 55 years of age had a documented FSH level $\geq$ 35 mIU/mL; or,
 - c. surgically postmenopausal (bilateral oophorectomy or hysterectomy); or
 - d. sterile (surgically [bilateral tubal ligation] or the Essure Procedure). Female volunteers that were surgically sterile or surgically postmenopausal were to provide documentation of the bilateral tubal ligation, bilateral oophorectomy, or hysterectomy prior to Period I patch application or the volunteer agreed to use a medically acceptable non-hormonal method of birth control. The Essure

Procedure must have been inserted at least 3 months prior with documentation of the Essure confirmation test prior to Period I patch application. If the procedure was inserted less than 3 months prior to Period I patch application or proper documentation of the confirmation test was not provided, the volunteer agreed to use an additional non-hormonal medically acceptable method of birth control.

7. Was willing to shower using the same soap/cleaners from the Screening Visit through the end of the study.
8. Was willing to follow study restrictions.

Exclusion Criteria

1. Anyone who reported receiving any investigational drug within 28 days prior to Period I patch application.
2. Anyone who reported any presence or history of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, hepatic, immunologic, hematologic, endocrine, or neurologic system(s) or psychiatric disease as determined by the Investigator(s).
3. Anyone who had a presence of any clinically significant results from laboratory tests, vital signs assessments, and ECGs, as judged by the Investigator(s).
4. Anyone who demonstrated a systolic blood pressure less than 90 mmHg or greater than 160 mmHg; a diastolic blood pressure less than 50 mmHg or greater than 95 mmHg; or a heart rate less than 50 beats per minute or great than 100 beats per minute, after a 5 minute rest in supine position at the screening visit.
5. Anyone who demonstrated a clinically relevant finding, as determined by the Investigator(s), on the screening ECG, such as second- or third-degree atrioventricular block or complete bundle branch block.
6. Anyone who, when confirmed upon additional testing, demonstrated a reactive screen for hepatitis B surface antigen, hepatic C antibody, or HIV antibody.
7. Anyone who demonstrated a positive drug screen.
8. Anyone who reported a clinically significant illness during the 28 days prior to Period I patch application (as determined by the Investigators).
9. Anyone who reported a history of allergic response(s) to rivastigmine, other carbamate derivatives, any component of the transdermal system, or related drug.
10. Anyone who reported a history of clinically significant allergies including food or drug allergies; sensitivity or allergy to adhesive bandages, tapes or transdermal systems; significant allergy to soaps, lotions, emollients, ointments, creams, cosmetics, adhesives, or latex.
11. Anyone who reported a history of drug or alcohol addiction or abuse within the past 1 year.
12. Anyone who reported a history or presence of clinically significant skin disorders (such as, but not limited to, skin cancer, psoriasis, vitiligo, or atopic dermatitis); obvious difference in skin color between application sites; presence of excessive hair (volunteers that agreed to have their hair clipped [not shaved] prior to patch application were eligible), shaved or depilated skin, cuts, open sores, tattoos, piercing, branding, rash, scarring, or recent heavy exposure to sun resulting in sunburn at the intended site of application. Basal cell carcinomas that were superficial and did not involve the investigative sites were allowable.

13. Anyone who reported a history of any medical conditions that may alter skin appearance, such as diabetes and porphyria.
14. Anyone who reported a history of sick sinus syndrome, conduction defects (sinoatrial block, atrioventricular block) gastroduodenal ulcerative conditions, asthma, or chronic obstructive pulmonary disease, urinary obstruction, or extrapyramidal symptoms such as tremor or seizures.
15. Anyone who reported donating blood within 28 days prior to Period I patch application. All subjects were advised not to donate blood for 4 weeks after completing the study.
16. Anyone who donated plasma (e.g., plasmapheresis) within 14 days prior to Period I patch application. All subjects were advised not to donate plasma for 4 weeks after completing the study.
17. Anyone who demonstrated, in the opinion of study staff, veins unsuitable for repeated venipuncture (e.g., veins difficult to locate, access, or puncture; veins with a tendency to rupture during or after puncture).
18. Anyone who reported difficulty fasting or consuming standardized meals.
19. Females who were pregnant, lactating, breastfeeding, or intended to become pregnant over the course of the study.
20. Females who demonstrated a positive pregnancy screen.
21. Anyone who reported smoking or using tobacco products or was currently using nicotine products (patches, gums, etc.). Thirty-day (30) abstinence was required.

Reviewer's Comment: *The inclusion/exclusion criteria are acceptable.*

Procedures and Observations:

Subjects were dosed sequentially, in groups of 3 (e.g., Subjects 01 – 03) at 2-minute intervals beginning at 0830 hours with 1 topical patch application to the upper back by a non-blinded study staff according to the randomization scheme. The patch was worn for a 24-hour period and then was removed by a non-blinded technician. Taping of the patch was not allowed throughout the conduct of the study. Dosing was completed as scheduled.

The following activities occurred in preparing the application sites:

- Subjects were instructed to shower the evening before patch application. Subjects were instructed not to use any kind of soap during the shower. No shower was permitted from hours prior to patch application until after patch removal.
- Subjects were instructed not to use any creams, lotions, powders, or other products (including any kind of medicated or non-medicated soap) on the application sites at any time during the study period.
- Prior to any application, the site was gently washed with room temperature water and patted dry with a dry tissue or similar material. The application site must have been completely dry (at least 15 minutes) following wash) before any patch application.
- The application area should not have been oily, damaged, or irritated. Any excess hair at the application site was clipped (not shaved).
- The application site (upper back) was marked prior to patch application.

Patch Application

The following activities occurred in applying the patch:

- At each study period, subjects received single dose consisting of 1 patch of the assigned formulation applied to the designated area of the skin. The patch was applied to clean, dry, intact skin on the upper back. The exact application site was noted on each subject's source documents and demarcated with a soft-tipped indelible marker on the upper back.
- The patch was applied on the designated application site immediately after the patch was removed from the outer package (the package was opened by hand or scissors, whichever was necessary). The clear plastic protective backing (release liner) from the patch was removed, and the patch was placed sticky (adhesive) side down on the prepared skin site in the demarcated area. Caution was taken not to touch the adhesive side at any time during the patch application process. During removal of the release liner from the patch, precaution was taken not to allow the patch to stick to itself. If the patch stuck to itself, that patch was discarded and another one was used instead.
- The patch was firmly pressed into place with the palm of the hand and held for a minimum of 30 seconds. The patch was to be in good contact with the application site, especially around the edges and the center. The patch was smoothed out after application to ensure no air bubbles were entrapped under the surface of the patch. The date and time of application was recorded.
- Taping or any external reinforcement of the patch was not allowed throughout the conduct of the study.

Patch Application Period

The following activities and/or restrictions occurred during the patch application period:

- Subjects were recommended to wear loose-fitting clothing (such as a loose-fitting t-shirt) during the course of the study. No clothing that was excessively heavy, binding, tight, rough/hard (such as denim), or rubbed against the patch application site was worn over the application site during the course of the study.
- Subjects were instructed not to touch, scratch, or rub the patch or application area.
- Subjects were instructed to keep the patch as dry as possible by completely avoiding showers, steam baths, and soaking during the wear period. During the 24-hour wear period, subjects were permitted to wash (e.g., with a damp cloth) provided they did not get the patch wet.
- Subjects did not apply heat (such as heating pads or electric blankets) or cold compresses (such as ice packs) to the patch application site from 2 hours prior to patch application and throughout the 24 hour wear period.
- After scoring the adhesion of the patch, any patch that showed detachment was not pressed back by applying pressure to the lifted portion of the patch. The condition of the patch's application/adhesion was documented. Additional comments regarding patch application may have been included. Occurrences of any redness or irritation around the patch application site were observed and documented.
- If for any reason, excessive irritation or a burning sensation occurred at or around the patch application site and the Investigator felt that the patch had to be removed due to safety concerns for that particular subject, the patch was removed and the subject was withdrawn from further participation in the study.
- Subjects were reminded to let staff know if a patch was peeling off or not adhering (for any reason including subject scratching patch), if a patch got wet, or if any other

experiences occurred related to the patch (pain, itching, or burning on or around the application area). If a patch fell off, study staff was to be notified immediately and the subject and study staff were to ensure that no one came into contact with patch except for study staff. Clinical staff were to make a note of exactly what time the patch came off and under what conditions. For subjects whose patch came off completely before 24 hours, a decision was made following discussion between the clinical site and the Sponsor with regard to continuation or discontinuation of the subject in the study. In such cases the patch was not replaced.

Subjects remained seated for the first 4 hours after patch application except as otherwise required for study procedures or personal needs. Subjects were not allowed to sit in unusual seating postures that may have mechanically promoted patch detachment. Subjects were not allowed to lie down (except as directed by clinical staff secondary to AEs) for the first 11 hours after patch application. Strenuous activity was prohibited throughout all research center confinement periods.

Patch Removal

The following activities occurred during patch removal:

- The patch was removed immediately following safety monitoring, adhesion assessment, and blood sampling procedures at the 24-hour post-dose time point.
- The removal of the patch was done carefully and slowly to avoid causing dermal irritation.
- After the patch was removed, the used system was placed adhesive side down on the oversized release liner provided by the sponsor. The used patch was placed on the side of the release liner that read: “stick patch on this side”. The patch was then placed in a Ziploc bag and sealed. The Ziploc bag was marked with the protocol number, subject number, treatment period, and date and time of removal. The Ziploc bag was stored at controlled room temperature.
- In addition, a total of 6 control samples (3 test and 3 reference samples) were prepared for residual drug analysis in manner identical to used study patches above, but were marked as Test Control 1, 2, or 3; or Reference Control 1, 2, or 3.
- At the end of the study, all control and used patches, including any systems worn by subjects who may have dropped out of the study early, were sent for analysis by courier to:



Randomization:

The randomization scheme used to assign each subject number to a treatment sequence was generated by Cetero Research – Fargo. The randomization scheme utilized a 2-treatment, 2-sequence design and was generated prior to the first dosing period using SAS software (version 9.2 or higher). The sequence of drug administration (AB or BA) was generated in a 1:1 ratio. Half of the subjects were scheduled to receive treatment A followed by treatment B, and the other half were scheduled to receive treatment B followed by treatment A. Each

subject number was pre-assigned a treatment sequence. The randomness of the assignment to treatment was ensured by assigning the subject numbers on a first come/first served basis.

Blinding:

Neither the dosing staff nor the subjects were blinded. However, the staff involved in monitoring the subjects, collecting subjective and objective data, and querying the subjects on AEs were blinded, as much as possible, to the product source under evaluation to maintain study integrity. The randomization code was not available to the bioanalytical facility.

Criteria for removal from the study:

If for any reason, excessive irritation or a burning sensation occurred at or around the patch application site and the Investigator felt that the patch had to be removed due to safety concerns for that particular subject, the patch was removed and the subject was withdrawn from further participation in the study.

Reviewer's Comment: The study design and procedures for evaluating the patch adhesion are acceptable and consistent with the draft guidance.

Prior and Concomitant Therapy:

Once the study began, only the medication described in the protocol was taken for the duration of the study. If for medical reasons, any drug was administered during the study, the Investigator recorded and notified the Sponsor of all information.

Compliance:

The subjects were monitored throughout the confinement portion of the study. Dosing was completed by the Cetero Research staff to ensure treatment compliance and proper drug administration.

Safety Measures

Safety measurements were obtained at the discretion of the Investigator in addition to the following safety assessments illustrated in Table 26.

Table 26: Clinical Laboratory Tests

CBC with Differential ^{a,c}	Clinical Chemistry ^{a,c}	Urinalysis ^a
- Hemoglobin - Hematocrit - White blood cell count with differential - Red blood cell count - Platelet count	- BUN - Creatinine - Total bilirubin - Alkaline phosphatase - AST (SGOT) - ALT (SGPT) - Glucose (fasting) - Albumin - Total protein	- pH - Specific gravity - Protein - Glucose - Ketones - Bilirubin - Blood - Nitrites - Leukocytes - Urobilinogen - Microscopic urine analysis if dipstick positive
Urine Drug Screen ^{a,d}	Serology Screen ^{a,d}	Additional Test(s)
- Amphetamines - Barbiturates - Cannabinoids - Cocaine metabolites - Opiates - Phencyclidine - Ethyl alcohol - Benzodiazepines	- HIV test - HBsAg - HCV	- Serum Pregnancy test (females only)^{a, b, c, d} - FSH^{a, e}

^a Screening; ^b Check-in (each period); ^c Exit/Early Termination; ^d Any subject with a positive result was excluded from the study; ^e If necessary to document postmenopausal status.

The subjects were monitored throughout the confinement portion of the study. Additional measurements were obtained at the discretion of the Investigator(s) or clinical staff. The Investigator or qualified medical designee was on-site for dosing and available by cell phone throughout the study.

Physical examinations were performed at screening and at study exit.

All vital signs throughout the study were measured after a 5 minute rest in a supine position. Blood pressure, heart rate, respiratory rate, and oral temperature were measured at screening. Blood pressure and heart rate were measured prior to patch application (within 90 minutes) and at approximately 12 and 24 hours ($\pm$ 60 minutes) after patch application. Blood pressure, heart rate, and temperature were measured at study exit or early termination.

An ECG was recorded at screening.

Blood samples were collected at screening, each check-in (females only), and at study exit. Urine samples were collected at screening.

Adverse Event Evaluation

The staff recorded all AEs observed, queried, or spontaneously volunteered by the subjects. Subjects who experienced AEs were followed until the event(s) resolved to the satisfaction of the

Investigator(s). Any serious AE was reported to the Sponsor within 24 – 48 hours of discovery. If the event was also unexpected, life-threatening, or fatal, the event was also

reported to the IRB. Subjects withdrawn from the study due to any AEs were followed until an outcome was determined. All AEs, regardless of severity, were recorded in the appropriate section of the case report forms (CRFs).

All bioavailability and safety measurements described are commonly used in this type of study, and are generally recognized as reliable, accurate, and relevant. Repeated vital sign measurements were obtained post patch application (12 and 24 hours after each patch application) in order to encompass the anticipated time of peak plasma levels and the elimination phase for rivastigmine. These data were intended to provide additional safety information. Adhesion was evaluated at 0 (immediately following patch application) 2, 4, 6, 8, 10, 12, 18, and 24 hours ($\pm$ 10 minutes) after patch application.

2.4.4.1.2 Endpoints

Skin Adhesion Assessment:

The primary objective related to adhesion was whether the level of adhesion of the test patch type was non-inferior to that of the reference patch type.

A 5-point, ordinal, categorical scale was used to measure adhesion in this study:

0 = 90% or more adhered (essentially no lift off of the skin)

1 = 75% to <90% adhered (some edges only lifting off of the skin)

2 = 50% to <75% adhered (less than half of the system lifting off of the skin)

3 = < 50% adhered but not detached (more than half the system lifting off of the skin but not detached)

4 = patch detached (patch completely off the skin)

***Reviewer's comment:** The adhesion assessment scale used in the study is acceptable; it is consistent with the one recommended in the draft guidance.*

Irritation Evaluation:

There were no specific criteria for irritation evaluation.

2.4.4.1.3 Statistical analysis plan

Pharmacokinetic (PK) and statistical analyses were performed for plasma rivastigmine data. Data from subjects who completed the study were included in the pharmacokinetic analyses. Data from subjects with missing concentration values (missed blood draws, lost samples, samples unable to be quantitated) were used if PK parameters could be estimated using the remaining data points. Otherwise, concentration data from these subjects were excluded for the final analysis.

Analysis Population:

Per Protocol Patch Population for Adhesion

All patches with completed adhesion scores for subjects that completed the study with no major protocol deviations/non-compliance were included in the Per Protocol Patch Population for Adhesion (PPPA).

If a patch completely detached prior to 24 hours, a decision was made following discussion between the clinical site and the Sponsor with regard to continuation or discontinuation of the subject in the study. In either case, the patch was not replaced. If the subject continued in the study, a score of 4 was carried forward for all further assessments for that specific patch.

Those patches removed early for unacceptable irritation or for those subjects that dropped out of the study or withdrew from the study before the end of the 24 hour application were not included in the PPPA.

All patches that had at least 1 adhesion score measured constituted the Intent-to-Treat Patch Population for Adhesion (ITTPA). The ITTPA was a pure data set with no last observation carried forward (LOCF) with the exception of data where there was complete patch detachment.

Adhesion Analysis:

The primary endpoint of adhesion was the following:

The cumulative total adhesion score during the 24 hour application period (i.e., total adhesion score for a specific subject and patch type was the sum of the adhesion scores recorded at [immediately after patch application], 2, 4, 6, 8, 10, 12, 18, and 24 hours [$\pm$ 10 minutes] after application of each patch type). The PPPA was used in this analysis.

The primary objective related to adhesion was whether the level of adhesion of the test patch type was non-inferior to that of the reference patch type. Because the attachment measurement cumulative adhesion score (CAS) shows a better attachment for lower values, the relevant hypotheses were:

$H_0: \mu_T - 1.25\mu_R > 0$ (not non-inferior)

$H_1: \mu_T - 1.25\mu_R \leq 0$ (non-inferior)

The relevant non-parametric hypotheses were:

$H_0: \text{median}_T - 1.25\text{median}_R > 0$ (not non-inferior)

$H_1: \text{median}_T - 1.25\text{median}_R \leq 0$ (non-inferior)

The adhesion evaluation of the active test and reference product must have demonstrated that the upper bound of the 1-sided 95% CI of the mean cumulative adhesion score for the test product (μ_T) minus 1.25 times the mean cumulative adhesion score for the reference product (μ_R) be less than or equal to 0, as per the hypotheses above.

The primary analysis for this study was determined based on the distribution of the CAS data. An ANOVA model was first run where CAS was treated as the dependent variable. Sequence, period, and treatment were treated as fixed effects and subject nested in sequence as a random effect. The residuals from this model were inspected for normality and subjected to a Shapiro-Wilk test. Q-Q plots of the residuals were also used for a visual

assessment of the normality. If the residual data from the ANOVA was shown to be normally distributed, then parametric methods of analysis were carried out and used as the primary analysis to assess the non-inferiority of the adhesion level of test and reference. If the data appeared to be non-normally distributed, the non-parametric methods were carried out and used as the primary analysis and the parametric analysis was used as supportive evidence. In either case, the secondary analysis was included in the report for information purposes.

Non-Parametric Methods

If the total CAS were shown not to be normally distributed, the analysis of relative differences between the test and reference scores using parametric methods would be inappropriate because small absolute differences in insignificantly low test and reference scores become more inflated on the relative scale than on the absolute scale compared to higher scores. In this case, the adhesion scores of the reference group were scaled by multiplying the individual total CAS by 1.25 prior to application of the non-parametric test. The 95% bootstrap CI of the median individual difference between test and scaled reference was used for evaluating non-inferiority. The Wilcoxon Signed-Rank Test was also presented.

Parametric Methods

If the total CAS were shown to be normally distributed, then the primary analysis was performed using parametric methods.

The ANOVA model used above to assess normality was used to create the upper bound of the 1-sided 95% CI of the mean CAS for the test product (μ_T) minus 1.25 times the mean CAS for the reference product (μ_R). If the 95% 1-sided upper bound of $\mu_T - 1.25\mu_R$ was less than 0, then non-inferiority of the test product compared to the reference product in CAS was concluded.

No prospective calculations of statistical power were made.

***Reviewer's Comment:** The Sponsor's adhesion analysis is acceptable, it is consistent with the draft guidance.*

Irritation Analysis:

There was no specified analysis for irritation.

***Reviewer's Comment:** The protocol stated that at the time of the patch's application/adhesion assessment, additional comments regarding patch application, occurrences of any redness or irritation around the patch application site were observed and documented.*

Safety Analysis:

Descriptive statistics was used for the safety analysis.

Missing values or Dropouts:

Adhesion data from subjects who completed the study were included in the final adhesion data analysis. If a patch completely detached prior to 24 hours, a decision was made following a discussion between the clinical site and the Sponsor with regard to continuation or discontinuation of the subject in the study. In either case, the patch was not replaced. If the subject continued in the study, a score of 4 was carried forward for all further assessments for that specific patch.

Those patches removed early for unacceptable irritation or for those subjects that dropped out of the study or withdrew from the study before the end of the 24 hour application were not included in the PPPA.

Changes to Planned Analysis:

No changes in the planned conduct of the study or planned analyses occurred.

2.4.4.2 Study Conduct

Discussion of Patient Populations:

Forty-one (41) volunteers checked in for Period I and a total of 30 subjects were enrolled. The study was conducted with 30 (27 completed) healthy adults. Subjects checked into the clinical facility on 11 November 2011 for Period I and on 18 November 2011 for Period II. Check-in occurred on the day prior to dose administration. The subjects remained confined at the clinical facility until after the 36-hour blood sample collection on study days 2 and 9.

Three subjects were discontinued from the study (Subject ^{(b) (6)}) due to AEs (nausea, vomiting, and/or headache); all of these subjects were discontinued before the end of the Period I. They were included into the safety analysis; however, were excluded from the PK analyses.

Table 27 below summarizes disposition the study population.

Table 26: Summary of Subject Disposition by Sequence

	Sequence		Total
	AB	BA	
Subjects Who Received at Least One Dose	15	15	30
Subjects Who Completed the Study	13	14	27
Subjects Who Elected to Withdraw	2	1	3
Subjects Excluded from Final PK Analysis	2	1	3
Subjects Excluded from the PPPA Analysis	2	1	3

Protocol Deviations

There were several non-significant deviations that did not affect the results of the study.

Retention of Reserve Samples:

The clinical investigators maintained drug records CRFs, and signed subject consent documents for at least 5 years from the time the drug is marketed unless instructed in writing by the Sponsor that records may be destroyed or forwarded to the Sponsor. In accordance with federal Regulations and ICH-GCP guidelines, these records will be available for inspection and copying if requested by a properly authorized regulatory agent.

It was the responsibility of the Sponsor to ship a sufficient number of dosage units to allow the clinical research facility to maintain an appropriate sampling on-site as per federal requirements. Drug supplies used for reserve samples segregated from the dosing supply, were stored in a secure storage location with restricted access, under conditions consistent with product labeling.

The remaining dosage units will be retained in a secure environment for the appropriate period of time as per federal requirements.

Demographics and Baseline Characteristics:

Table 27: Demographics of the Enrolled Study Population (N=30)

Age	Mean Range	43.4 ± 14.9 18 – 63
Sex	Male Female	8 (26.7%) 22 (73.3%)
Ethnicity/Race	American Indian or Alaskan Native	1 (3.33%)
	Asian	1 (3.33%)
	Black or African American	1 (3.33%)
	White/Not-Hispanic	26 (86.67%)
	White and American Indian or Alaskan Native	1 (3.33%)

2.4.4.3 Results

Adhesion:

All patches with completed adhesion scores for subjects that completed the study with no major protocol deviations/non-compliance were included in the Per Protocol Patch Population for Adhesion (PPPA).

All patches that had at least one adhesion score measured constituted the Intent-to-Treat Patch Population for Adhesion (ITTPA). The ITTPA was a pure data set with no last observation carried forward (LOCF) with the exception of data where there was complete patch detachment.

PPPA consisted of 27 subjects for each treatment group. ITTPA consisted of 29 subjects for Treatment A and 28 subjects for Treatment B. Among those who had detachments, all but one subject (b) (6) in Treatment A had scores of 1. Subject (b) (6) had the highest score of 2.

A total of six subjects (6/27, 22.2%) in Treatment A had at least once a score of ≥ 1 during the study, whereas a total of 7 (7/27, 25.9%) such subjects were in Treatment B group. Tables 29 through 32 summarize the Sponsor's results.

Table 28: Summary of Cumulative Adhesion Scores – PPPA (The Sponsor's analysis)

	Test Product A: Rivastigmine Transdermal System, 9.5 mg/24 hours	Reference Product B: Exelon Patch, 9.5 mg/24 hours
N	27	27
Arithmetic Mean	0.70	0.52
Standard Deviation	1.49	1.05
Median	0.00	0.00
Max	0.00	0.00
Min	6.00	4.00

Table 29: Frequency of Adhesion Scores – PPPA (The Sponsor's analysis)

Treatment	Score	Hour 0	Hour 2	Hour 4	Hour 6	Hour 8	Hour 10	Hour 12	Hour 18	Hour 24
A	0	27 (100.00%)	27 (100.00%)	27 (100.00%)	27 (100.00%)	25 (92.59%)	24 (88.89%)	23 (85.19%)	21 (77.78%)	24 (88.89%)
	1	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.41%)	3 (11.11%)	4 (14.81%)	6 (22.22%)	2 (7.41%)
	2	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)
	3	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	4	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
B	0	27 (100.00%)	27 (100.00%)	27 (100.00%)	27 (100.00%)	26 (96.30%)	24 (88.89%)	26 (96.30%)	22 (81.48%)	23 (85.19%)
	1	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	3 (11.11%)	1 (3.70%)	5 (18.52%)	4 (14.81%)
	2	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	3	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	4	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

The Sponsor's analyses of the results:

To demonstrate non-inferiority of Test Product A, Rivastigmine Transdermal System, 9.5 mg/24 hours, compared to Reference Product B, Exelon Patch, 9.5 mg/24 hours, with regards to CAS, the scores for Reference Product B were first scaled by multiplying the individual total CAS by 1.25. The pair wise difference between the Test and scaled Reference CAS were then computed for each subject. Bootstrap simulations (10,000 datasets) were then performed using a sampling with replacement technique from this dataset. The bootstrap median for each dataset was calculated and an overall one sided upper 95% confidence interval was constructed based on the ranked medians.

The 95% bootstrap upper bound confidence limit (1-sided) of the median difference between Test Product A and Reference Product B is shown in Table 31.

Table 30: Summary of 95% Bootstrapping Confidence Limit – CAS (PPPA – N=27)

Variable	Median Difference	Upper Bound of 95% Bootstrap Confidence Limit of the Median Difference
Cumulative Adhesion Scores (Test – 1.25*Reference)	0.00	0.00

The upper bound for the 95% confidence limit was equal to zero which indicates that Test Product A, Rivastigmine Transdermal System, 9.5 mg/24 hours, was non-inferior to the Reference Product B, Exelon Patch, 9.5 mg/24 hours.

Given the paired nature of data, the Wilcoxon Signed Rank Test was also used to assess the statistical significance in the difference between the CAS of Test Product A, Rivastigmine Transdermal System, 9.5 mg/24 hours, and the scaled CAS of Reference Product B, Exelon Patch, 9.5 mg/24 hours. Table 32 summarizes the results of the adhesion analysis using Wilcoxon Signed Rank Test, using the CAS.

Table 31: Statistical Results of Adhesion Analysis Using Wilcoxon Signed Rank Test – CAS (PPPA – N=27) (The Sponsor’s Analysis)

Variable	Hypotheses	Test Statistic	p-value
Cumulative Adhesion Scores (Test – 1.25*Reference)	H ₀ : Median _T – 1.25Median _R > 0 H ₁ : Median _T – 1.25Median _R ≤ 0	-149.5	0.2004

The Wilcoxon Signed Rank Test statistic was negative and the p-value for this test was greater than 0.05, which indicates that Test Product A, Rivastigmine Transdermal System, 9.5 mg/24 hours, was not statistically different to that of the scaled Reference Product B, Exelon Patch, 9.5 mg/24 hours.

Reviewer’s Comment: *The proportion of subjects developing a score of at least 1 for detachment was similar for the test product compared to the RLD (6 vs. 7 subjects). There was only one subject with the score of 2 in the Test product A arm. This degree of detachment is not significant. There was no difference between the treatments on how early into the treatment the detachment occurred; both treatment arms had the first subject with the score of 1 at the 8th hour.*

The sponsor’s defined ITTPA population is not acceptable. It differs from the PPPA population because it included subjects that withdrew from the study prior to 24 hour evaluation. If the subject removed the patch prior to completion of the 24 hour treatment period, it should not be included in the patch adhesion evaluation. None of the three subjects withdrawn from the study had detachments of the patch recorded, but they may have had if they would have stayed in the study.

There were a total of nine evaluation time points during the 24 hour treatment periods. This is helpful for determining how early into the application period detachment occurs; however, too many assessment scores may dilute the overall results.

Final analysis should use PPPA population. The FDA statistician was asked to verify the sponsor's methods and results. There were several subjects ((b) (6) in the RLD group (B), and (b) (6) in the test group (A)) that had detachments (scores of "1") at hours 8, 10, or 18 but a score of "0" at hour 24. The analysis should be revised, all subsequent scores after they had "1" for these subjects should be listed as "1", not "0", for the "24 hour."

Summary of the FDA Statistical Review on adhesion

The initial analysis was performed using methods recommended in the Draft Guidance on Rivastigmine. Following conclusion was made by the reviewer: "Non-inferiority analyses based on the mean cumulative adhesion scores (primary endpoint) showed that the one-sided 95% upper bound for confidence limit for the adjusted mean difference ($\mu_T - 1.25\mu_R$) was greater than zero and the non-inferiority test was not passed for test versus reference patch. Therefore, the adhesion potential of the test is not non-inferior to that of the reference."

However, based on the Memorandum "Waiver Statistical Non-Inferiority Analysis for Highly Adhering Drug Products dated 2/10/2014 by Bryan Newman, Ph.D. (see this memo in the Appendix 2), the adhesion data in the study R10-1307 was reconsidered. Summary of the FDA's analyses is provided in Tables 33 and 34.

Table 32: Frequency of adhesion scores (PPPA) using LOCF data

Treatment	Score	Hour 0	Hour 2	Hour 4	Hour 6	Hour 8	Hour 10	Hour 12	Hour 18	Hour 24
Test	0	27 (100.00%)	27 (100.00%)	27 (100.00%)	27 (100.00%)	25 (92.59%)	24 (88.89%)	22 (81.48%)	20 (74.07%)	20 (74.07%)
	1	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.41%)	3 (11.11%)	5 (18.52%)	7 (25.93%)	6 (22.22%)
	2	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)
	3	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	4	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Reference	0	27 (100.00%)	27 (100.00%)	27 (100.00%)	27 (100.00%)	26 (96.30%)	24 (88.89%)	24 (88.89%)	21 (77.78%)	20 (74.07%)
	1	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	3 (11.11%)	3 (11.11%)	6 (22.22%)	7 (25.93%)
	2	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	3	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	4	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Table 33: Waiver Analysis for Test and the RLD

Product	Visit	Percentage of Patches with Score=0	Average
Test	Hour 0	27/27 = 100%	90.1%
	Hour 2	27/27 = 100%	
	Hour 4	27/27 = 100%	
	Hour 6	27/27 = 100%	
	Hour 8	25/27 = 92.6%	
	Hour 10	24/27 = 88.9%	
	Hour 12	22/27 = 81.5%	
	Hour 18	20/27 = 74.1%	
	Hour 24	20/27 = 74.1%	
Reference	Hour 0	27/27 = 100%	91.8%
	Hour 2	27/27 = 100%	
	Hour 4	27/27 = 100%	
	Hour 6	27/27 = 100%	
	Hour 8	26/27 = 96.3%	
	Hour 10	24/27 = 88.9%	
	Hour 12	24/27 = 88.9%	
	Hour 18	21/27 = 77.8%	
	Hour 24	20/27 = 77.8%	

The reviewer concluded that based on data in Table 34, “the test and reference products meet the adhesion criterion of 90/90 ($\geq 90\%$ of patches having $\geq 90\%$ adhesion throughout the entire study). Based on “ Memo for Statistical Non-inferiority Analysis for Highly Adhering Patch Drug Products”, the adhesion study should be permitted to waive the requirement of passing the NI statistical test- since meeting those conditions is sufficient evidence for demonstrating high adhesion.”

Irritation:

There were no AEs related to the patch application site reported.

2.4.5 Comparative Adhesion Conclusion

Data from the study #R10-1307 demonstrate that there is no difference in adhesion properties between the new proposed generic patch and the RLD Exelon® patch.

2.4.6 Comparative Irritation Conclusion

Non-inferiority analyses based on the mean cumulative irritation scores (primary endpoint) showed that the one-sided 95% upper confidence limit for the adjusted mean difference ($\mu_T - 1.25\mu_R$) was less than zero and the non-inferiority test was passed for test patch versus reference patch. Therefore, the irritation potential of the test patch is not worse than that of the reference patch.

2.4.7 Comparative Sensitization Conclusion

The Sponsor provided sufficient evidence that sensitization potential of Alvogen's Rivastigmine TDS is not worse than that of the RLD Exelon® patch.

2.5 Comparative Review of Safety

2.5.1 Brief Statement of Conclusions

Overall, AEs reported during the Alvogen's drug development program are consistent with the side effects of topical application of rivastigmine. There was no difference in frequency, severity, or the type of AEs reported between the proposed generic drug and the RLD.

A total of 310 subjects were exposed to the Alvogen's rivastigmine patch in two clinical studies.

In study C10-1870, a total of 280 subjects were exposed to rivastigmine (daily dose of 4.6 mg/24 hours). No SAEs were reported over the course of this study. One subject was discontinued and one subject withdrew from the study due to AEs. One subject was discontinued due to a positive urine pregnancy test result. Skin reaction AEs (application site discharge, application site irritation, application site pain, and application site pruritus) were reported by 75 (26.79%) subjects and 69 (24.64%) subjects during treatment with Rivastigmine TDS, 4.6 mg/24 hours and Exelon® Patch, 4.6 mg/24 hours, respectively. Overall, the most frequently reported systemic AEs (reported by 3 or more subjects) were: abdominal pain, diarrhea, nausea, application site irritation, application site pain, application site pruritus, fatigue, nasopharyngitis, dizziness, headache, somnolence, insomnia, oropharyngeal pain, and rhinorrhea.

In study R10-1307, a total of 30 subjects were enrolled and 27 completed the study. Safety population included all 30 subjects. In this cross-over single dose study, all subjects received one 9.5 mg/24 hours, RLD and the test, patch.

No serious AEs were reported over the course of this study. Overall, the most common AEs reported were nausea (7 (23.3%) subjects), headache (4 (13.33%) subjects), vomiting (3 (10%) subjects), and abdominal discomfort (2 (6.67%) subjects). All of these events were considered by the Investigator to be possibly or likely related to the treatments. There was no difference in the number or type of AEs reported between the two treatment arms. Only nausea was reported more frequently in the reference treatment arm.

2.5.2 Description of Adverse Events for Patch Skin Irritation and Sensitization Study (Study C10-1870 (R10-1318, S11-0069))

Subjects who successfully completed the study were exposed 21 times to a 24-hour application and once to a 48-hour application of Rivastigmine Transdermal System, 4.6 mg/24 hours and 21 times to a 24-hour application and once to a 48-hour application of Exelon Patch, 4.6 mg/24 hours. In each case, the dose given was a half patch application of each treatment (both worn simultaneously for 24 or 48 hours) x 4.6 mg/24 hours for a total

of ~101.2 mg of drug exposure throughout study conduct per subject. Table 35 summarizes the extent of exposure.

Table 35: Extent of Exposure for All Dosed Subjects

Treatment Dose	Number of Subjects	Total Number Doses Applied	Total Exposure Per Subject
Subjects Who Completed the Study (n-230)			
½ x 4.6 mg/24 hours transdermal system of Test Product and ½ x 4.6 mg/24 hours transdermal system of Reference Product, both applied simultaneously for 24 hours ± 1 hour	230	21	~96.6 mg
½ x 4.6 mg/24 hours transdermal system of Test Product and ½ x 4.6 mg/24 hours transdermal system of Reference Product, both applied simultaneously for 48 hours ± 4 hours	229	1	~4.6 mg
Discontinued Subjects			
½ x 4.6 mg/24 hours transdermal system of Test Product and ½ x 4.6 mg/24 hours transdermal system of Reference Product, both applied simultaneously for 24 hours ± 1 hour	1	21	~96.6 mg
½ x 4.6 mg/24 hours transdermal system of Test Product and ½ x 4.6 mg/24 hours transdermal system of Reference Product, both applied simultaneously for 48 hours ± 4 hours	1	1	~4.6 mg
½ x 4.6 mg/24 hours transdermal system of Test Product and ½ x 4.6 mg/24 hours transdermal system of Reference Product, both applied simultaneously for 24 hours ± 1 hour	16	21	~96.6 mg
	1	20	~92.0 mg
	1	19	~87.4 mg
	2	18	~82.8 mg
	2	17	~78.2 mg
	3	16	~73.6 mg
	1	15	~69.0 mg
	1	13	~59.8 mg
	1	11	~50.6 mg
	2	10	~46.0 mg
	3	9	~41.4 mg
	2	8	~36.8 mg
	2	7	~32.2 mg
	4	6	~27.6 mg
	3	5	~23.0 mg
3	4	~18.4 ng ⁵	
3	2	~9.2 mg	

One hundred twenty-five subjects reported a total of 458 AEs across all treatments over the course of the study. The AEs were mild to moderate in intensity; no SAEs were reported. One subject was discontinued and 1 subject withdrew from the study due to AEs. Subject (b) (6) was dropped from the study due to a migraine and Subject (b) (6) elected to withdraw from study due to AEs (abdominal discomfort and diarrhea). A total of 107 mild and 62 moderate AEs were attributed to the administration of Rivastigmine TDS, 4.6 mg/24 hours, a total of

⁵ Units describing dose are listed as ng instead of mg; this may have been a typo error.

91 mild and 62 moderate AEs were attributed to the administration of Exelon® Patch, 4.6 mg/24 hours, and a total of 124 mild and 12 moderate AEs were unable to be attributed to a specific treatment. All AEs were followed until resolution.

Table 36 displays the most frequently (reported by 3 or more subjects) reported AEs (coded by MedDRA Version 14.1 preferred term) by treatment arm. Since both treatments were administered at the same time, most adverse events could not be attributed to a specific treatment, except for application site disorders.

Table 36. Frequently Reported Adverse Events by Treatment Arm (The Sponsor's analysis)

Adverse Event (AE) MedDRA SOC / Preferred Term*	Treatment Arm		
	Test Product A: Rivastigmine Transdermal System, 4.6 mg/24 hours N=280	Reference Product B: Exelon Patch, 4.6 mg/24 hours N=280	**Not Attributed to a Specific Treatment N=280
Gastrointestinal disorders			
Abdominal pain	-	-	3 (1.07%)
Diarrhea	-	-	4 (1.43%)
Nausea	-	-	15 (5.36%)
General disorders and administration site conditions			
Application site irritation	59 (21.07%)	57 (20.36%)	-
Application site pain	7 (2.50%)	5 (1.79%)	-
Application site pruritus	25 (8.93%)	20 (7.14%)	1 (0.36%)
Fatigue	-	-	9 (3.21%)
Infections and infestations			
Nasopharyngitis	-	-	3 (1.07%)
Nervous system disorders			
Dizziness	-	-	5 (1.79%)
Headache	-	-	11 (3.93%)
Somnolence	-	-	4 (1.43%)
Psychiatric disorders			
Insomnia	-	-	4 (1.43%)
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	-	-	8 (2.86%)
Rhinorrhoea	-	-	8 (2.86%)

*MedDRA Version 14.1

Overall, skin reaction AEs (application site discharge, application site irritation, application site pain, and application site pruritus) were reported by 75 (75/280) subjects (26.79%) and 69 (69/280) subjects (24.64%) during treatment with Rivastigmine TDS, 4.6 mg/24 hours and Exelon® Patch, 4.6 mg/24 hours, respectively.

The number of subjects reporting most commonly reported systemic AEs in decreasing frequency are displayed below (denominator – 280 enrolled subjects):

- 15 (5.36%) nausea
- 11 (3.93%) headache
- 9 (3.21%) fatigue
- 8 (2.85%) oropharyngeal pain, rhinorrhea

- 5 (1.79%) dizziness
- 4 (1.43%) insomnia, somnolence
- 3 (1.07%) abdominal pain, nasopharyngitis
- 2 (0.71%) diarrhea, vomiting, decreased appetite, depressed mood, nightmare, cough, nasal congestion

Except for AEs related to the respiratory system, all other AEs were considered by the Investigator to be possibly related to the treatments administered and were unable to be attributed to a specific treatment.

Two subjects were discontinued from the study due to AEs:

- Subject (b) (6) was dropped from the study by the Investigator prior to Day 7 patch application due to an AE (migraine). Migraine was considered by the Investigator to be moderate in intensity and not related to the study treatments and was unable to be attributed to a specific treatment.
- Subject (b) (6) elected to withdraw from the study prior to Day 36 activities due to AEs (abdominal discomfort and diarrhea). AEs of diarrhea and abdominal discomfort were both considered by the Investigator to be mild in intensity and not related to the study treatments. Both AEs were unable to be attributed to a specific treatment.

Subject (b) (6) a 24 year old white female, was dosed with one-half patch of Test Product A, Rivastigmine TDS, 4.6 mg/24 hours and one-half patch of Reference Product B, Exelon® Patch, 4.6 mg/24 hours both applied daily to separate sites on the upper arms (right or left upper arm) for 24 hours ± 1 hour on Days 1 – 15 (b) (6). Urine pregnancy testing was completed at screening and on Day 1, 8 and 15. The results of the urine pregnancy test at screening and on Day 1 and 8 were negative. Subject (b) (6) completed a urine pregnancy test on Day 15, was patched with the study products on Day 15 at 16:28 hours and after patching it was determined that the results of the urine pregnancy collected on Day 15 were positive. The study products were removed at 17:22 hours on Day 15 and a serum pregnancy test was collected; the subject was then dropped from the study. Attempts were made to contact the subject via telephone on (b) (6) and were unsuccessful. A certified letter was sent to the subject on (b) (6) and was returned as undeliverable on (b) (6). The subject was lost to follow-up on (b) (6).

Reviewer's Comment: *The outcome of pregnancy for subject (b) (6) is not known.*

Overall, the adverse event profile for rivastigmine in this trial seems to be relatively benign and consistent with the posted label. There were no serious AEs reported. The most important information pertinent to this application is a local safety assessment for both patches. There was no difference in a rate or severity of local AEs between the two treatment groups.

Since both patches (generic and RLD) were administered together, it is not possible to attribute the reported systemic AEs to one or the other treatment. Therefore, systemic AEs reflect rivastigmine's effects overall. The most common AE reported during this trial –

nausea – was also the most commonly observed AE (>5%) during double-blind efficacy trials for the RLD.

This trial did not reveal any new safety signals for rivastigmine and further supports overall safety of a transdermal rivastigmine patch.

2.5.3 Description of Adverse Events for Patch Adhesion Study (Study R10-1307)

A total of 30 subjects were enrolled and 27 completed the study. Safety population included all 30 subjects.

No serious AEs were reported over the course of this study.

Overall, the most common AEs reported were nausea, headache, vomiting, and abdominal discomfort. Nausea was reported on at least 1 occasion in 7 (7/30) subjects (23.33%) and was considered by the Investigator to be likely related to the treatments on 7 occasions and possibly related to the treatments on 1 occasion. Headache was reported on at least 1 occasion in 4 (4/30) subjects (13.33%) and was considered by the Investigator to be likely related to the treatments on 6 occasions. Vomiting was reported on at least 1 occasion in 3 (3/30) subjects (10.00%) and was considered by the Investigator to be likely related to the treatments on all occasions. Abdominal discomfort was reported on 1 occasion in 2 (2/30) subjects (6.67%) and was considered by the Investigator to be likely related to the study treatments.

Three (3) subjects withdrew from the study due to AEs:

- Subject (b) (6) elected to withdraw from the study prior to Period I, study hour 11 activities due to AEs (nausea, vomiting, and headache).
- Subject (b) (6) elected to withdraw from the study prior to Period I, study hour 9 activities due to an AE (nausea).
- Subject (b) (6) elected to withdraw from the study prior to Period I, study hour 10 activities due to AEs (nausea and vomiting).

Table 37: Frequently Reported Adverse Events by Treatment Arm

Adverse Event (AE) MedDRA SOC / Preferred Term ⁺	Treatment Arm	
	Test Product A: Rivastigmine Transdermal System, 9.5 mg/24 hours N = 29	Reference Product B: Exelon Patch, 9.5 mg/24 hours N = 28
Gastrointestinal disorders		
Abdominal discomfort	1 (3.45%)	1 (3.57%)
Nausea	3 (10.34%)	5 (17.86%)
Vomiting	2 (6.90%)	2 (7.14%)
Nervous system disorders		
Headache	3 (10.34%)	3 (10.71%)

MedDRA Version 14.1; SOC = System Organ Class

Reviewer's Comment: Adverse events reported (nausea, vomiting, headache, and abdominal discomfort) during this study are consistent with those reported in other trials with rivastigmine. There was no significant difference in the number or type of AEs reported

between the two treatment arms. Only nausea was reported more frequently in the reference treatment arm.

2.6 Relevant Findings From Other Consultant Reviews

2.6.1 Review of the DSI Report

There were two study sites for the study C10-1870 (R10-1318, S11-0069):

1. Study site #1 (Dr. A. Copa) has been inspected on 2/3/2012 for another ANDA (202346) and was found to be acceptable. Therefore, a new inspection was not requested.
2. Study site #2 (Dr. Freeman) has an unsatisfactory inspection history (b) (4). On May 21, 2013, OSI provided their evaluation of the FDA audit of the clinical portions of two studies for (b) (4), conducted at PRACS Institute (Cetero Research, Principal Investigator: James C. Freeman), St. Charles, MO, during (b) (4) by ORA investigators Kathleen B. Swat and Karen M. Montgomery (Kansas District Office). OSI provided the following conclusions:

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

Because of these findings, DCR requested a For-Cause inspection for Dr. James C. Freeman (Site #02). Results of this inspection are pending at this time.

2.6.2 Review of the FDA Statistical Report

Please refer to the detailed statistical review by the FDA statistician Gyoing Sun, entered in DARRTS on 5/28/2014.

2.7 Formulation

Transdermal matrix delivery system

2.7.1 Generic Drug Product Design

Rivastigmine transdermal system (Rivastigmine-TDS) is a matrix patch consisting of two matrix layers. It is available in two strengths, 4.6 mg/24 hr and 9.5 mg/24 hr. The compositions of both strengths are the same and the only difference is the patch size. The patches are a circular shape.

The reservoir layer consists of an acrylate-vinylacetate matrix forming agent and dispersed rivastigmine free base as the active ingredient. Acrylate-vinylacetates are well known in pharmaceutical preparations including transdermal matrix patches.

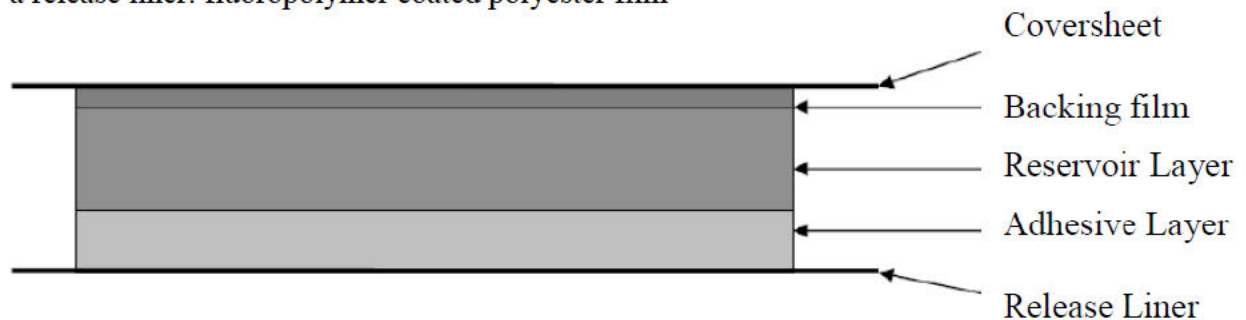
A polyisobutene based adhesive layer comprising polymers of two different molecular weight polyisobutenes is used in the adhesive matrix. The light mineral oil is fixed into the adhesive layer with a small portion of Colloidal Silicon Dioxide NF.

An impermeable backing liner made from aluminum coated polyester combined with skin colored polyethylene has been chosen to protect the patch from the environment. The patch is situated on a standard release liner with fluoropolymer-coating. This liner is removed prior to application.

After manufacturing each transdermal patch, together with a cover sheet made of polyethylene terephthalate siliconized on one side, is individually packed into a (b) (4) (b) (4)

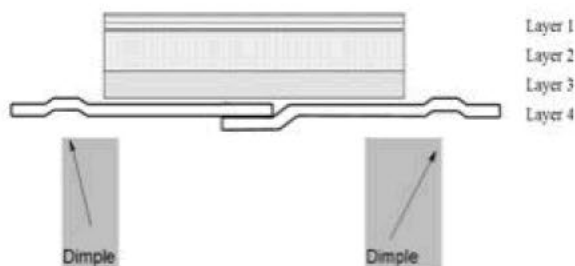
(b) (4) -TDS is composed as shown in the following schematic drawing:

- a cover sheet: siliconized polyethylene terephthalate film
- a backing liner: Polyethylene / thermoplastic resin / aluminum coated polyester film
- an adhesive matrix layer
- a release liner: fluoropolymer coated polyester film



2.7.2 RLD Product Design

The RLD, Exelon Patch, patch comprises a four-layer laminate containing the backing layer, drug matrix, adhesive matrix and overlapping release liner. The release liner is removed and discarded prior to use. See Figure 1 for a detailed illustration.



- Layer 1 Backing Film
- Layer 2 Drug Product (Acrylic) Matrix
- Layer 3 Adhesive (Silicone) Matrix
- Layer 4 Release Liner (removed at time of use)

Excipients within the formulation include acrylic copolymer, poly(butylmethacrylate, methylmethacrylate), silicame adhesive applied to a flexible polymer backing film, silicone oil, and vitamin E.

Table 38 below summarizes the differences between the proposed drug and the RLD.

Table 38: Comparison between the Generic Drug and the RLD Exelon® Patch

Labeled Strength	Generic Patch			RLD – Exelon Patch		
	4.6 mg/24 hr	9.5 mg/24 hr	13.3 mg/24 hr	4.6 mg/24 hr	9.5 mg/24 hr	13.3 mg/24 hr
Total amount of rivastigmine	6.9 mg	13.8 mg	20.7 mg	9.0 mg	18.0 mg	27 mg
Size	4.6 cm ²	9.2 cm ²	13.8 cm ²	5 cm ²	10 cm ²	15 cm ²

Reviewer’s comment: The sizes of the proposed generic patches are smaller and the total amounts of the active ingredient are lower compared to the corresponding patches of the RLD. As long as the drug’s absorption rate and extent are the same as the RLD’s, therapeutically these patches should be equivalent and the public safety risk of residual drug will be less.

The backing film in the proposed generic patch is aluminum coated. In 2009, FDA posted a safety alert on the risk of burns with certain medicated patches when worn during MRI scans.⁶ Since aluminum is contained only in the backing film, which has to be removed before the patch is applied,

(b) (4)

(b) (4)

(b) (4)

⁶ <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm142815.htm>

2.7.3 Components & Composition

Table 39: Composition of the Drug Product

Component	Function	4.6 mg/24 hr Amount mg / 4.6 cm ²	9.5 mg/24 hr Amount mg / 9.2 cm ²	13.3 mg/24 hr Amount/ Patch Size: 13.8 cm ²	IIG Database Limit for Transdermal Products
Active layer, target area weight: (b) (4)					
Rivastigmine	API	6.9 mg	13.8 mg	20.7 mg	N/A
(b) (4)					

¹ Removed during the manufacturing process and is not present in the final product

Reviewer's Comment: *None of the inactive ingredients in the proposed drug product exceed the IIG Database Limits for Transdermal Products, therefore, should be considered safe.*

2.8 Conclusion and Recommendation

2.8.1 Conclusion

Safety and adhesion of the proposed generic rivastigmine transdermal system is acceptable for approval. Submitted data demonstrated that the generic patch is no more irritating, no more sensitizing and adheres at least as well as the RLD Exelon patch. Even though the skin irritation/sensitization study evaluated only the lower strength (4.6 mg/24 hours) of the patch, there is no reason to believe that the higher strengths would have a different dermal safety profile. Adhesion assessment was done only for the 9.5 mg/24 hours patch. However, since all three proposed patches are proportionally similar in their formulation, safety and adhesion data could be extrapolated to all three strengths.

2.8.2 Recommendations

From the clinical safety perspective, this ANDA should be approved, pending satisfactory OSI inspection, CMC, Labeling, comparative bioavailability data, and any other relevant regulatory assessment.

The backing film in the proposed generic patch is aluminum coated. In 2009, FDA posted a safety alert on the risk of burns with certain medicated patches when worn during MRI scans. Since aluminum is contained only in the backing film, which has to be removed before the patch is applied, (b) (4)

(b) (4)

CLINICAL BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 204403

APPLICANT: Alvogen Pine Brook, Inc.

DRUG PRODUCT: Rivastigmine Extended Release Film 4.6 mg/24 hours; 9.5 mg/24 hours and 13.3 mg/24 hours

The Division of Clinical Review has completed its review of your skin irritation, sensitization, and adhesion data **based on the information available prior to the Office of Scientific Investigation (OSI) inspection findings** and has no further questions at this time. The Division of Clinical Review recommends that the skin irritation, sensitization, and adhesion data submitted to ANDA 204403 are adequate to support approval of the application based on information available prior to OSI inspection findings.

Please note that the clinical bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

John R. Peters, M.D.
Director, Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research

{See appended electronic signature

Ethan M. Stier, Ph.D., R.Ph.
Director, Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

Appendix 1. Draft Guidance on Rivastigmine

Recommended studies: 2 studies

1. Type of study: Bioequivalence (BE) with Pharmacokinetic (PK) Endpoints and Adhesion Study Design: Single-dose, two-treatment, two-period crossover in vivo Strength: 9.5 mg/24 hr Subjects: Healthy males and nonpregnant females, general population Additional comments: The transdermal patch should be applied to clean, dry, hairless, intact healthy skin on the upper back, chest, or upper arm, as recommended in the approved reference listed drug (RLD) labeling and worn for 24 hours.
2. Type of study: Skin Irritation and Sensitization Study Design: Randomized, evaluator-blinded, in vivo, within-subject repeat test Strength: 4.6 mg/24 hr (Dose: One-half of 4.6 mg/24 hr patch) Subjects: Healthy males and nonpregnant females, general population. Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Rivastigmine in plasma (PK study only)

Bioequivalence based on (90% CI): Rivastigmine (PK study only)

Waiver request of in vivo testing: 4.6 mg/24 hr and 13.3 mg/24 hr based on (i) acceptable BE study on the 9.5 mg/24 hr strength, (ii) acceptable dissolution testing of all strengths, and (iii) proportional similarity in the formulations across all strengths.

Dissolution test method and sampling times: Please note that a Dissolution Methods Database is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Development of an independent dissolution method is encouraged if the FDA recommended method is not suitable for the test product. In addition, dissolution testing using multi-pH media (pH 1.2, 4.5, and 6.8 buffer) should be conducted. Multipoint dissolution profiles should be obtained using a discriminating agitation speed. A surfactant may be used with appropriate justification. Specifications will be determined upon review of the data submitted in the application.

Additional comments regarding the BE with PK endpoints and adhesion study:

1. Adhesion performance of the intact test and RLD patches must be formally evaluated and compared in the BE with PK endpoints and adhesion study or in a separate parallel or crossover adhesion study of single 24-hour patch applications of the active test product versus the RLD. No patch reinforcement is allowed when the study is being used to establish adequate adhesion performance to support product approval. Adhesion scoring is to be performed at least daily, in this case just prior to removal at the end of a 24-hour application. For patches that completely detach, a score of 4 should be carried forward in the adhesion analysis for all remaining observations in the application period.
2. The recommended scoring system for adhesion of transdermal patches is indicated as follows:
0 = $\geq$ 90% adhered (essentially no lift off the skin)
1 = $\geq$ 75% to $<$ 90% adhered (some edges only lifting off the skin)
2 = $\geq$ 50% to $<$ 75% adhered (less than half of the patch lifting off the skin)
3 = $>$ 0% to $<$ 50% adhered but not detached (more than half of the patch lifting off the skin without falling off)
4 = 0% adhered - patch detached (patch completely off the skin)
3. The Per-Protocol (PP) Population evaluation of the adhesion parameter should be defined per patch instead of per subject as follows:

Adhesion Analysis – should include all patches except those removed early for unacceptable irritation or those that dropped out of the study before the end of the 24-hour application.

4. The adhesion score and the time from application until patch detachment (i.e., duration of patch wear) should be evaluated for the test product and RLD, and a statistical analysis of the comparative results should be performed. In addition, the following adhesion data should be provided for the test product and RLD:
 - a. frequency table showing the number of patches with each adhesion score at each evaluation time point
 - b. number of patches that are completely detached at each evaluation time point

The adhesion evaluation of the active test product and RLD must demonstrate that the upper bound of the one-sided 95% CI of the mean adhesion score for the test product minus 1.25 times the mean adhesion score for the RLD must be less than or equal to 0. For the adhesion evaluation, the Office of Generic Drugs (OGD) also considers the number of subjects that experience detachment or unacceptable adhesion scores and how early in the application period those unacceptable scores are observed.

The same mean score could be reached with a small number of high scores (e.g., ≥ 3) as with a larger number of low scores (e.g., 1, which are of little clinical significance). Thus, it is difficult to determine the clinical meaningfulness of a given mean score or a given difference between products with regard to mean scores. Therefore, in addition to mean scores, it is necessary to also evaluate the proportion of subjects with a meaningful degree of detachment for each product. The proportion of subjects with a meaningful degree of detachment should be no higher for the test product than for the RLD, and detachment should not occur earlier in the application period for the test than for the RLD. To be approved, the test product must be non-inferior with regard to mean adhesion scores and also show no meaningful difference with regard to degree of detachment.

5. For the Adhesion Analysis, please provide a separate line listing for each individual test article per subject, per each visit (if data exist), using the following headings, if applicable:
 - a. Subject identifier
 - b. Treatment: test article (i.e., test product, RLD)
 - c. Period (i.e., patch was applied during Period 1 or Period 2)
 - d. Application Sequence Number: number of particular test article application (i.e., 1=first, 2=second)
 - e. Location of Dose Administration: individual test article application site
 - f. Number of days since baseline visit
 - g. Application date and time
 - h. Date and time of removal or complete detachment
 - i. Duration of Treatment: time (hours) from individual test article application to removal or complete detachment
 - j. Included in PP population for adhesion analysis (yes/no)
 - k. Reason for exclusion from PP population for adhesion analysis
 - l. Scoring date
 - m. Adhesion scores
 - n. Identity of the evaluator
 - o. Was the patch reinforced with tape or overlay (yes/no)
 - p. If patch was reinforced, time from patch application to reinforcement

Additional comments regarding the skin irritation and sensitization study:

1. The OGD recommends evaluating skin irritation and sensitization in a single study. To support approval, the test product must be no more irritating than the RLD and be no more sensitizing than the RLD. Each parameter is to be evaluated with a separate analysis. The primary endpoints should be considered as co-primary endpoints, e.g., for each of them, the study must demonstrate that the test product is no worse than the RLD. The analysis for each parameter and the primary endpoint(s) and any secondary endpoint(s) for each analysis are to be clearly defined in the protocol prior to the start of the study. A clear, objective definition of a sensitization reaction is also to be pre-specified in the protocol.
2. Due to safety concerns, it is not recommended to simultaneously apply two whole, active, 4.6 mg/24 hr rivastigmine patches on the same subject during the 21-day skin irritation and sensitization study. The optimum design of this study will depend on the design of the test product patch. Since the RLD has a matrix design that can be safely cut in half, one half of the patch can be used for these studies. If the test product

patch also has a design that can be cut to a smaller size, it should also be cut in half and one half of the test product patch applied simultaneously with one half of a RLD patch (to separate skin sites). It would not be acceptable to manufacture a separate batch of product in order to use a smaller patch in this study.

3. Cutting patches will change the shape and size of the patch and may alter the adhesive performance. Therefore, if partial patches are used for the skin irritation and sensitization study, the OGD recommends collecting adhesion data in the BE with PK endpoints and adhesion study to demonstrate that the test product adheres at least as well as the RLD for the 24-hour duration of wear. To do so, no reinforcement may be applied to patches in the BE with PK endpoints and adhesion study. Alternatively, a separate single-application parallel or crossover design adhesion study may be conducted for the 24-hour duration of wear, comparing the un-altered to be marketed test product and RLD.
4. If the test product patch has a reservoir design that cannot be cut in half, then, in order to avoid an unacceptable risk of serious adverse events, the study should be conducted using a parallel design with subjects randomized to receive either the test product or RLD. The study should be powered to show that the test is no more irritating, no more sensitizing, and adheres at least as well as the RLD.
5. The recommended study consists of two phases, a 21-day Induction Phase, followed by a 14 to 17 day rest period, and a Challenge Phase.

During the Induction Phase, all test articles (i.e., one-half of the 4.6 mg/24 hr test product¹, one-half of the 4.6 mg/24 hr RLD, one-half of the optional vehicle patch² and optional negative control³) are to be applied simultaneously to each subject at different sites, with sequential patch applications to the same skin sites every 24 hours (the intended duration of wear) for a total of 21 consecutive days. The patches should be applied to clean, dry, hairless, intact healthy skin on the upper back, chest, or upper arm, as recommended in the approved reference listed drug (RLD) labeling. Thus, it is recommended to apply the patches daily on Days 1-21 to the same sites and to have each of them remain in place for 1 day (a total of 21 days altogether). The Day 21 patches would be removed on Day 22. The irritation evaluation is to be conducted during the Induction Phase, with assessment of “Dermal Response” and “Other Effects” at the time of each patch change.

The Challenge Phase consists of a single 48-hour application of one-half of the 4.6 mg/24 hr test product, one-half of the 4.6 mg/24 hr RLD, one-half of the optional vehicle patch and the optional negative control to a naïve site followed by an assessment of “Dermal Response” and “Other Effects” at 30 minutes and at 24, 48, and 72 hours after challenge patch removal, with a narrative description of any reactions observed, together with the opinion of the investigator as to whether such reactions are felt to be indicative of a contact sensitization. A re-challenge test four to eight weeks following the original challenge, conducted in the same manner, is recommended for all subjects with a potential sensitization reaction.

6. An adequate number of subjects should be enrolled to ensure that at least 200 evaluable subjects are included in the PP population.
7. The irritation and adhesive properties may be sensitive to climate conditions. Therefore, the OGD prefers that the study be conducted in multiple centers with different climate conditions.
8. Subjects should not apply make-up, creams, lotions, powders, or other topical products to the skin area where the patch will be placed, as this could affect adhesive performance or irritation potential.
9. Assignment of the test product, RLD, optional vehicle patch, and optional negative control to skin sites should be randomized. The method of randomization should be described in the protocol. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity for each application site on each subject.
10. Please refer to 21 CFR 320.38, 320.63 and the Guidance for Industry, “Handling and Retention of BA and BE Testing Samples”, regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of bioequivalence testing. In addition, the investigators should follow the procedures

of 21 CFR 58 and ICH E6, “Good Clinical Practice: Consolidated Guideline”, for retention of study records and data in order to conduct their studies in compliance with Good Laboratory Practices (GLP) and Good Clinical Practices (GCP). Retention samples should be randomly selected by each drug site prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.

11. Inclusion Criteria (the sponsor may add additional criteria):
 - a. Healthy male and female subjects 18-65 years of age inclusive.
 - b. Subject has a normal screening ECG; non-specific ST-T wave changes are acceptable.
12. Exclusion Criteria (the sponsor may add additional criteria):
 - a. Subject is pregnant or lactating.
 - b. Clinically relevant findings in screening 12-lead ECG, such as second- or third-degree atrioventricular block or complete bundle branch block.
 - c. Systolic blood pressure < 90 or >160 mmHg at screening measured in supine position after 5 minutes rest; diastolic blood pressure <50 or >95 mmHg at screening measured in supine position after 5 minutes rest; heart rate <50 or >100 at screening.
 - d. Medical history of sick sinus syndrome, conduction defects (sino-atrial block, atrioventricular block), gastroduodenal ulcerative conditions, asthma or chronic obstructive pulmonary disease, urinary obstruction, extrapyramidal symptoms such as tremor or seizures.
 - e. Medical history of condition that would significantly influence the immune response (e.g., primary or acquired immunodeficiencies such as human immunodeficiency virus (HIV) positive or AIDS, allergic diseases such as anaphylaxis, asthma or generalized drug reaction, neoplasms such as lymphoma or leukemia, rheumatoid arthritis or systemic lupus erythematosus).
 - f. Medical history of significant dermatologic diseases or conditions, such as atopy, psoriasis, vitiligo or conditions known to alter skin appearance or physiologic response (e.g. diabetes, porphyria).
 - g. History of significant dermatologic cancers (e.g. melanoma, squamous cell carcinoma), except basal cell carcinomas that were superficial and did not involve the investigative site.
 - h. Within 3 weeks prior to dosing, use of cholinergic compounds.
 - i. Within 3 weeks prior to dosing, use of medications or treatments that would significantly influence or exaggerate responses to the test product or that would alter inflammatory or immune response to the product (e.g. cyclosporine, tacrolimus, systemic or topical corticosteroids, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin (BCG), monoclonal antibodies, radiation therapy).
 - j. Within 72 hours prior to dosing, use of antihistamines or use of topical drugs at patch site.
 - k. Subject has an obvious difference in skin color between arms or the presence of a skin condition, excessive hair at the application sites, scar tissue, tattoo, or coloration that would interfere with placement of test articles, skin assessment, or reactions to drug.
 - l. Presence of open sores at the application site.
13. Provide a listing of the prescription and over-the-counter drug products that are contraindicated during the study, such as:
 - a. Nonsteroidal anti-inflammatory drugs (NSAIDs)
 - b. Other cholinomimetic drugs
 - c. Anticholinergic medications
 - d. Succinylcholine-type muscle relaxants during anesthesia
 - e. Use of medications or treatments that would significantly influence or exaggerate responses to the test product or that would alter inflammatory or immune response to the product (e.g. antihistamines, systemic or topical corticosteroids, cyclosporine, tacrolimus, cytotoxic drugs, immune globulin, Bacillus Calmette-Guerin (BCG), monoclonal antibodies, radiation therapy).
14. Subjects should be advised to avoid exposing the patch application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.
15. Subjects should be advised that if they need to have surgery during the study, they should inform their doctor that the rivastigmine transdermal patch may exaggerate the effects of some muscle relaxants during anesthesia.

16. Subjects should be advised that the rivastigmine transdermal patch may cause dizziness and drowsiness, mainly at the start of treatment or when increasing the dose. Subjects should be advised that if they feel dizzy or drowsy, they should not drive, operate machines or perform any other tasks that require attention.
17. During the induction phase, subjects should return for daily visits on Days 2-21 for adhesion scoring, patch removal, irritation scoring, and patch replacement and on Day 22 for adhesion scoring, patch removal and irritation scoring. After wearing the challenge patch for 48 hours (or until removal due to intolerable reaction), subjects should return for adhesion scoring, patch removal and irritation scoring at 30 minutes and at 24, 48, and 72 hours after challenge patch removal. Scoring of patch adherence and skin reactions should be performed by a trained and blinded observer at each patch removal. All efforts should be made to ensure that the same scorer is used for all observations. If the same scorer is not used in all cases, inter-scorer variability needs to be addressed in the protocol, specifying the training and standards for each score.
18. Due to likely differences in appearance of the patches, blinding of the observer/evaluator may not be possible, especially for evaluation of patch adhesion, which requires direct observation of the patch itself. However, efforts should be made to blind the evaluation of irritation and sensitization.
19. To ensure adequate adhesion of the test articles, adhesion scores are to be recorded just prior to patch removal. The recommended scoring system for adhesion of transdermal patches is indicated as follows:
 0 = $\geq$ 90% adhered (essentially no lift off the skin)
 1 = $\geq$ 75% to $<$ 90% adhered (some edges only lifting off the skin)
 2 = $\geq$ 50% to $<$ 75% adhered (less than half of the patch lifting off the skin)
 3 = $>$ 0% to $<$ 50% adhered but not detached (more than half of the patch lifting off the skin without falling off)
 4 = 0% adhered - patch detached (patch completely off the skin)
20. During both the Induction Phase and Challenge Phase, the skin reactions are to be evaluated and scored according to the following two scales:

Scale 1: Dermal Response

Skin Appearance	Score
No evidence of irritation	0
Minimal erythema, barely perceptible	1
Definite erythema, readily visible; or minimal edema; or minimal papular response	2
Erythema and papules	3
Definite edema	4
Erythema, edema, and papules	5
Vesicular eruption	6
Strong reaction spreading beyond test (i.e., application) site	7

Scale 2: Other Effects

Observation	Score (Numeric equivalent)
Slightly glazed appearance	A (0)
Marked glazed appearance	B (1)
Glazing with peeling and cracking	C (2)
Glazing with fissures	F (3)
Film of dried serous exudates covering all or part of the patch site	G (3)

Small petechial erosions and/or scabs	H (3)

When an “Other Effects” score is observed, each score should be reported as a number and letter combination score and also as a numerical total (i.e. numerical “Dermal Response” score + numeric equivalent for the “Other Effects” lettered score).

21. For subjects who experience irritation consistent with a combined score of ≥ 3 , or who experience symptomatic intolerable irritation, the patch may be moved to a new site in order to complete the 21-day Induction Phase and continue with the sensitization part of the study. In this circumstance the highest score observed (not truncated to 3) prior to discontinuation of the first patch site should be carried forward for all remaining observations in the irritation analysis.
22. Whereas this study using partial patches can not be used for a definitive assessment of adhesion performance of the active product, criteria may be established for using tape or an overlay to reinforce any patches that are lifting. This may be preferable to replacing detached patches, since shorter application intervals could give different irritation results. If the patch is reinforced with tape or an overlay, skin irritation associated with the tape or overlay area should be reported separately from that of the patch application area.
23. If a patch completely detaches, it should be replaced within 24 hours and the subject should continue in the study. During the 21-day Induction Phase, if a patch is completely detached for more than 24 hours (unless the patch was removed for an unacceptable degree of irritation), the subject should be excluded from both the irritation and sensitization analyses for that product. During the 48-hr Challenge Phase, if a patch is completely detached for more than 24 hours, the subject should be excluded from the sensitization analysis. The subject should note the date and time of detachment as soon as it occurs.

Safety Data and Analyses

24. All application site reactions are to be reported in the data tables and in the detailed narrative description for each subject’s response in both phases of this study in the study report. These would include subject complaints such as dryness, itching, burning, pain, or soreness, etc., identifying to which application site the complaint applies. These reports are to be compared between test articles.
25. The safety analyses should include all subjects who received a dose of study medication. Safety analyses should include comparing the test product, RLD, optional vehicle patch, and optional negative control with regard to the occurrence and severity of application site adverse events (AEs). Systemic drug-related AEs, change from baseline in blood pressure, and concomitant medications are also to be reported but cannot be distinguished between test articles.

Skin Irritation Data Tables and Analyses

26. For each day during the Induction Phase, when the skin is evaluated for irritation, please provide a frequency table showing the number of applications of each test article with each combined “Dermal Response” and “Other Effect” score using Last Observation Carried Forward for subjects who discontinued a test article because of unacceptable irritation. Please refer to Table 1 as an example.

Table 1: Number (%) of Applications by Induction Phase Day and Test Article with a Specific Combined “Dermal Response” and “Other Effect” Score

Induction Phase Scoring Day; Test Article	Combined “Dermal Response” and “Other Effect” Score										
	0	1	2	2A	2B	3	3A	3B	3C	3F	etc.
Day 2; Test Product											
Day 2; RLD											
Day 2; Vehicle Patch (optional)											
Day 2; Negative Control (optional)											

Day 3; Test Product											
Day 3; RLD											
etc.											

27. The Analysis Populations should be defined separately for each parameter and should be defined per patch instead of per subject. The PP Population for evaluation of skin irritation should be defined as follows:
Irritation Analysis– the test articles need to be applied sequentially to the same site for the entire 21 day induction phase (without any period of detachment longer than 24 hours) to be evaluated for the cumulative irritation effect OR if a patch is moved or removed due to excessive irritation, it should be included using Last Observation Carried Forward (LOCF).
28. For each test article (test product, RLD, optional vehicle patch and optional negative control), the mean cumulative irritation score is to be calculated as the sum of all combined “Dermal Response” and “Other Effects” scores observed at each observation divided by the total number of observations.
29. In addition to the cumulative irritation scores, the following data should be provided for each test article:
- Total number of observations with a combined “Dermal Response” and “Other Effects” irritation score of 3 or more for each product.
 - Number of patches that were moved or removed due to an unacceptable degree of irritation.
 - Number of days until sufficient irritation occurred to preclude repeat application to the same site.
30. To demonstrate non-inferiority of the test product compared to the RLD with regard to the cumulative irritation scores, the upper bound of the one-sided 95% CI of the mean test product score minus 1.25 times the mean RLD score must be less than or equal to 0. For the irritation evaluation, the OGD also considers other clinically relevant data including the number of applications that reach a maximal irritation score and the number of subjects that discontinue the product applications because of unacceptable irritation.

The same mean cumulative score could be reached with a small number of high scores (e.g., ≥ 3) as with a larger number of low scores (e.g., 1, which are of little clinical significance). Thus, it is difficult to determine the clinical meaningfulness of a given cumulative score or a given difference between products with regard to mean cumulative scores. Therefore, in addition to cumulative scores, it is necessary to also evaluate the proportion of subjects with a meaningful degree of irritation for each product. The proportion of subjects with a meaningful degree of irritation should be no higher for the test product than for the RLD, and irritation should not occur earlier in the application period for the test product than for the RLD. To be approved, the test product must be non-inferior with regard to cumulative irritation scores and also show no meaningful difference with regard to degree of irritation.

Sensitization Data Tables and Analyses

31. Please provide a frequency table showing the number of applications of each test article during the Challenge Phase with a specific combined “Dermal Response” numerical score and “Other Effect” letter score by each evaluation time point.
32. For all subjects with at least one combined score of 2 or more at 48 or 72 hours after patch removal in the Challenge Phase, please provide a table showing the actual scores for each subject at each evaluation time point during the Induction and Challenge Phases.
33. The Analysis Populations should be defined separately for each parameter and should be defined per patch instead of per subject. The PP Population for evaluation of sensitization should be defined as follows:

Sensitization Analysis – includes all test articles worn (without any period of detachment longer than 24 hours) for the full 21 day induction phase AND the entire 48-hour challenge phase AND the subject must return for at least one of the scheduled evaluations at 48 and 72 hours after removal of the challenge patch. If a test article is removed prior to the end of the 48-hour challenge phase due to an intolerable reaction, the application site should be evaluated at 24, 48, and 72 hours after patch removal and be included in the sensitization analysis using LOCF.

34. For each test article, individually evaluate each PP subject with a combined score of 2 or greater at 48 or 72 hours after patch removal during the Challenge Phase for potential sensitization. A narrative description of each reaction in the challenge phase should be provided, together with the opinion of the investigator as to whether such reactions are felt to be indicative of a contact sensitization. Consider a subject to be potentially sensitized if all of the following criteria are met:
- The subject has at least one evaluation occurring at more than 24 hours (e.g., at 48 or 72 hours) after the removal of the Challenge Phase patch.
 - The subject has a combined “Dermal Response” and “Other Effects” numeric score of at least 2 at their last evaluation during the Challenge Phase.
 - The combined “Dermal Response” and “Other Effects” numeric scores obtained during the Challenge Phase evaluations are generally higher than the combined “Dermal Response” and “Other Effects” numeric scores obtained during the Induction Phase.
 - If the subject completed a Rechallenge Phase, the above 3 criteria were met during both the Challenge Phase and the Rechallenge Phase.

Scores that resolve before 48 hours are generally considered to be due to irritation instead of sensitization. Provide the total number of subjects considered sensitized to the test product and RLD.

35. The sponsor should provide descriptive statistics comparing the proportion of subjects sensitized or potentially sensitized to each test article.

Adhesion Data Table

36. To ensure adequate skin contact for maximal induction of irritation and sensitization, please provide a frequency table showing the adhesion score for each patch per study visit. For patches that fall off, provide information about the duration of patch wear before the patch falls off.

Data Submission

37. Study data should be submitted to the OGD in electronic format.
- A list of file names, with a simple description of the content of each file, should be included.
 - Please provide a “pdf” document with a detailed description of the codes that are used for each variable in each of the SAS datasets (for example, Y=yes, N=no for analysis population).
 - All SAS transport files should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
 - Primary data sets should consist of two data sets: No Last Observation Carried Forward (NOLOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
 - Please provide a separate dataset for each study to include such variables as demographics, baseline admission criteria, baseline vital signs, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance and comments, etc.
38. Please provide a summary dataset containing a separate line listing for each test article per subject (if data exist) using the following headings, if applicable:
- Study identifier
 - Subject identifier
 - Site identifier: study center
 - Age
 - Age units (years)
 - Sex
 - Race
 - Name of Actual Treatment (exposure): test article (i.e., test product, RLD, optional vehicle patch and optional negative control)
 - Location of Dose Administration: patch application site
 - Duration of Treatment (total exposure in days) during Induction Phase: time from first application to discontinuation of test article during Induction Phase

- k. Duration of Treatment (total exposure in days) during Challenge Phase: time from first application to discontinuation of test article during Challenge Phase
- l. Per Protocol (PP) population inclusion for irritation analysis (yes/no)
- m. Reason for exclusion from PP population for irritation analysis
- n. PP population inclusion for sensitization analysis (yes/no)
- o. Reason for exclusion from PP population for sensitization analysis
- p. Test article moved (yes/no)
- q. Number of times test article moved
- r. Test article discontinued (yes/no)
- s. Reason for test article discontinuation
- t. Adverse event(s) reported for this treatment arm (yes/no)

Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of a summary dataset for each individual test article per subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXLOC	EXDURind	EXDURch	ppirr	ppirr_rs	ppsen	ppsen_rs	mv	mv_n	dis	dis_rs
101	1	01	54	YEARS	M	1	A	RUA	21	2	Y		Y		Y	1	N	
101	1	01	54	YEARS	M	1	B	LUA	21	2	Y		Y		Y	1	N	
101	2	01	45	YEARS	M	2	A	RUA	21	2	Y		N	B	N		N	
101	2	01	45	YEARS	M	2	B	LUA	21	2	Y		N	B	N		N	

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final dated 11/12/08.

- STUDYID: Study Identifier
- SUBJID: Subject Identifier for the Study
- SITEID: Study Site Identifier
- AGE: Age
- AGEU: Age units (years)
- SEX: Sex, e.g., M=Male, F=Female, U=Unknown
- RACE: Race, e.g. 1=White, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or Other Pacific Islanders
- EXTRT: Name of Actual Treatment (exposure), e.g. A=test product, B= RLD, C=optional vehicle patch, D=optional negative control
- EXLOC: Location of Dose Administration (exposure): specific anatomical site of patch application, e.g., RUA=right upper arm, LUA=left upper arm
- EXDURind: Duration of Treatment during Induction Phase (exposure in days; 21 days exposure planned during Induction Phase)
- EXDURch: Duration of Treatment during Challenge Phase (exposure in days; 2 days exposure planned during Challenge Phase)
- ppirr: Per Protocol (PP) population for irritation analysis, e.g., Y=Yes, N=No
- ppirr_rs: Reason for exclusion from PP population for irritation analysis, e.g., A=prematurely discontinued prior to completing irritation phase due to AE that was not intolerable irritation, B=failed to complete irritation phase due to lost to follow-up, C=failed to complete irritation phase due to subject moved out of the area, etc.
- ppsen: PP population for sensitization analysis, e.g., Y=Yes, N=No
- ppsen_rs: Reason for exclusion from PP population for sensitization analysis, e.g., A=prematurely discontinued prior to completing challenge phase due to AE that was not intolerable

irritation, B=failed to return for at least one of the two challenge visits at 48 and 72 hours, etc.

- mv: Test article moved, e.g., Y=Yes, N=No
- mv_n: Number of times test article was moved, e.g., 1, 2, 3, etc.
- dis: Discontinuation of the test article, e.g., Y=Yes, N=No
- dis_rs: Reason for test article discontinuation, e.g., A=irritation, etc.
- AErpt: Adverse event(s) reported for this treatment arm, e.g., Y=Yes, N=No

39. For the Irritation, Sensitization and Adhesion Analyses, please provide a separate line listing for each individual test article per subject, per each visit (if data exist) using the following headers, if applicable:

- a. Subject identifier
- b. Treatment: test article (i.e., test product, RLD, optional vehicle patch and optional negative control)
- c. Application Sequence: number of particular test article application (i.e., 1=first, 2=second, 3=third)
- d. Location of Dose Administration: test article application site
- e. Visit number
- f. Visit date
- g. Number of days since baseline visit
- h. Application day of week (i.e., Sunday, Monday, Tuesday, etc.)
- i. Application date and time
- j. Date and time of removal or complete detachment
- k. Duration of Treatment: time (hours) from individual test article application to removal or complete detachment
- l. Reason for exclusion of data from this individual test article from analysis
- m. Scoring date
- n. Adhesion score
- o. Induction “Dermal Response” numeric score for each site
- p. Induction “Other Effects” letter score for each site
- q. Challenge “Dermal Response” numeric score for each site
- r. Challenge “Other Effects” letter score for each site
- s. Potentially sensitized (yes/no)
- t. Identity of the evaluator
- u. Was the individual test article reinforced with tape or overlay (yes/no)
- v. If individual test article was reinforced, time from individual test article application to reinforcement
- w. Individual test article moved (yes/no)
- x. Number of times individual test article moved
- y. Date of each move of individual test article
- z. Individual test article discontinued (yes/no)
- aa. Reason for discontinuation
- bb. Date individual test article discontinued
- cc. Adverse event reported during this visit (yes/no)

Please refer to Table 3 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 3: Example of dataset containing one line listing for each individual test article per visit per subject

SUBJID	EXTRT	EXSEQ	EXLOC	VISITNUM	SVSTDTC	ELTMBS	day_wk	itaSTDTC	itaENDTC	itaDUR	exc_rs	scr_date	adh_2	adh_3	ind_n1	ind_cl
1	A	1	RUA	1	2004-07-01	1	Monday									

ind_n2	ind_c2	ind_n3	ind_c3	ch_n1	ch_c1	potsens	EVAL	reinf	reinf_tm	mv	mv_n	mv_dt1	mv_dt2	mv_dt3	dis	dis_rs	dis_dt	AErpt

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Draft dated 7/25/07.

SUBJID:	Subject Identifier for the Study
EXTRT:	Name of Actual Treatment (exposure), e.g. A=test product, B=RLD, C= optional vehicle patch, D=optional negative control
EXSEQ:	Sequence Number of exposure to particular test article (e.g. application number 1, 2, 3, etc.)
EXLOC:	Location of Dose Administration (exposure): specific anatomical site of patch application, e.g., RUA=right upper arm, LUA=left upper arm
VISITNUM:	Visit Sequence Number
SVSTDTC:	Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBL:	Elapsed Time since Baseline (days)
day_wk:	Day of week of individual test article application (i.e., Sunday, Monday, Tuesday, etc.)
itaSTDTC:	Individual test article application date and time: start date/time of individual test article
itaENDTC:	Individual test article removal date and time: end date/time of individual test article
itaDUR:	Individual test article exposure duration (hours) (i.e., time from individual test article application to removal)
exc_rs:	Reason for exclusion of data from this individual test article from analysis, e.g., A=subject did not show for appointment, B=test article detached for more than 24 hours, C=protocol/exclusion criteria violation, etc.
scr_date:	Scoring date
adh_2:	Adhesion score for Day 2
adh_3:	Adhesion score for Day 3 (etc. to Day 22)
ind_n1:	Numeric "Dermal Response" score for the first site during Induction
ind_c1:	Character "Other Effects" score for the first site during Induction
ind_n2:	Numeric "Dermal Response" score for the second site (if application site moved due to excessive irritation) during Induction
ind_c2:	Character "Other Effects" score for the second site during Induction
ind_n3:	Numeric "Dermal Response" score for the third site during Induction
ind_c3:	Character "Other Effects" score for the third site during Induction
ch_n1:	Numeric "Dermal Response" score for the Challenge site
ch_c1:	Character "Other Effects" score for the Challenge site
potsens:	Potentially sensitized
EVAL:	Evaluator: identity of the evaluator
reinf	Individual test article reinforced with tape or overlay e.g., Y=Yes, N=No
reinf_tm	If individual test article was reinforced, time (hours) from individual test article application to reinforcement
mv:	Individual test article moved, e.g., Y=Yes, N=No
mv_n:	Number of times individual test article was moved, e.g., 1, 2, etc.
mv_dt1:	Date of first move of individual test article
mv_dt2:	Date of second move of individual test article
mv_dt3:	Date of third move of individual test article
dis:	Discontinuation of the individual test article, e.g., Y=Yes, N=No
dis_rs:	Reason for individual test article discontinuation, e.g., A=irritation, etc.
dis_dt:	Date individual test article discontinued
AErpt:	Adverse Event reported during this visit, e.g., Y=Yes, N=No

40. Please note that the guidance provided here supersedes information provided in the Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products, which has been withdrawn.

The information given here is general in nature and represents the current thinking of the OGD for this product and may not be appropriate for other transdermal products.

Appendix 2.

Memo on Waiver of Statistical Non-Inferiority Analysis for Highly Adhering Patch Drug Products

MEMORANDUM

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

DATE: February 10, 2014

FROM: Bryan Newman, Ph.D.
ORISE Fellow, Science Staff
Office of Generic Drugs
Center for Drug Evaluation and Research

THROUGH: Robert Lionberger, Ph.D.
Acting Deputy Director for Science
Office of Generic Drugs
Center for Drug Evaluation and Research

TO: John Peters, M.D.
Director for the Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research

SUBJECT: Waiver of Statistical Non-Inferiority Analysis for Highly Adhering Patch Drug Products

Executive Summary

The FDA's recommended approach to establish non-inferiority (NI) of a generic patch's adhesive properties to that of the RLD uses linear mixed models, which carry the assumption that both the random effects model parameters and the residuals of the data follow a normal distribution. However, this approach is no longer appropriate for products that are highly adhering since the concentration of zero scores ($\geq 90\%$ attached) results in a highly right-skewed distribution. Performing a mixed model analysis to establish NI between a highly adhering generic and its highly adhering RLD often results in an inability to establish NI. Generics in this situation have little room to improve, since their adhesion profiles have reached the upper limits for adhesiveness, and so reach an inappropriate block to their approval.

To resolve this situation, products that meet or exceed $\geq 90\%$ of patches having $\geq 90\%$ adhesion throughout the entire study (defined as 90/90) can be said to have demonstrated a sufficiently adhesive product and can waive the current NI requirement. To support this waiver criterion, adhesion data from 15 ANDAs and their respective RLDs were

analyzed to determine which product could meet this condition. Of the 5 ANDAs that met the 90/90 criterion, 3 were at the upper limits of adhesiveness (98-100% of adhesion scores were zero, indicating $\geq 90\%$ adhesion) and all failed to establish NI using the recommended statistical method. Thus, waiving the statistical requirement of NI for these

products is appropriate given that, in terms of product quality, the generic patches demonstrated sufficient adhesive performance to permit approval.

Lastly, adhesion studies used to establish NI should contain a minimum of 60 subjects to qualify for the adhesion waiver. To determine the minimum sample size, adhesion data for each ANDA was bootstrapped (with replacement) to generate 5 sets of 10,000 studies, with each set using one of the sample sizes listed: 20, 36, 40, 60, 80 subjects. Results from the analysis showed that decreasing the number of subjects in the study increased the percentage of studies meeting the waiver criterion (i.e. increased the false positive rate). A sample size of 60 subjects maintained the false positive rate below 10%. Lastly, for products whose adhesion data is on the borderline of meeting the waiver criterion (89.0 to 89.9% average adhesion throughout the study duration), the product could be viewed as having met the waiver criterion if the study sample size is ≥ 60 , and no instances of poor product adhesion (i.e. no full detachments / adhesion scores = 4) are reported. This decision would be left for the clinical reviewer. Lastly, it is important to note that the minimum sample size is solely for the qualification of the adhesion waiver, and not for studies using the FDA recommended method for establishing NI.

FDA's Guidance for Conducting Adhesion Studies for Patch Drug Products

During the ANDA review process for topical and transdermal patch dosage forms, ANDA sponsors must ensure that the submitted generic meets both the standards for demonstrating bioequivalence and those that ensure product quality. For patch dosage forms, the tolerability and reliability of the adhesives used to retain the drug product on the skin are vital parameters in which the Agency gauges product quality. In terms of tolerability, patch irritation and sensitization are determined via trained observers that following inspection of the skin, record dermal (irritation) and other (sensitization) responses using the established FDA scoring system. In a similar fashion, patch reliability is assessed in terms of the adhesiveness of the patch throughout the labeled period of administration.

To compare the amount of detachment between the generic and RLD patches, each patch is first given an adhesion score that describes the amount of attachment to the skin at the time of observation, as assessed by a trained observer. The scoring system currently approved by the FDA is shown below.

Percent Attachment from Skin	Adhesion Score
$\geq 90\%$ Attached	0
$< 90\%$ to $\geq 75\%$ Attached	1
$< 75\%$ to $\geq 50\%$ Attached	2
$< 50\%$ to $\geq 25\%$ Attached	3
Complete Detachment	4

These scores are used to derive a mean adhesion score for a single patch for each subject. The number of adhesion measurements taken per patch is a function of the duration of wear; patches worn for 12 and 24 hours have one adhesion measurement whereas patches worn for 168 hours have seven adhesion measurements. A summary of all the

recommended measurement schedules contained in the bioequivalence guidance documents that measure adhesion is provided in Table 1.

Table 1. Summary of Patch Adhesion Sampling Regimes for Bioequivalence Guidance Documents with a Transdermal/Topical Route of Administration

Active Ingredient	RLD	Study	Total No. of TEST Patches	Length of Wear/Patch	Sampling Regime/Patch
Clonidine	18891	21-Day Induction Phase	3	168 hours (7 days)	Only take measurements on the <i>first</i> patch (See Item 3); daily measurements for 84 hours for a total of <u>4 measurements</u> (24, 48, 72, and 84 hours).
Estradiol	19081	21-Day Induction Phase	6	84 hours	Only take measurements on the <i>first</i> patch (See Item 19); daily measurements for 84 hours for a total of <u>4 measurements</u> (24, 48, 72, and 84 hours).
Estradiol	20375	21-Day Induction Phase	3	168 hours (7 days)	Only take measurements on the <i>first</i> patch (See Item 19); daily measurements for 7 days for a total of <u>7 measurements</u> (24, 48, 72, 96, 120, 144, and 168 hours).
Estradiol	21674	21-Day Induction Phase	6	84 hours	Only take measurements on the <i>first</i> patch (See Item 19); daily measurements for 84 hours for a total of <u>4 measurements</u> (24, 48, 72, and 84 hours).
Estradiol	20538	21-Day Induction Phase	6	84 hours	Only take measurements on the <i>first</i> patch (See Item 19); daily measurements for 84 hours for a total of <u>4 measurements</u> (24, 48, 72, and 84 hours).
Ethinyl Estradiol; Norelgestromin	21180	7-Day PK Bioequivalence	1	168 hours (7 days)	Daily measurements for 7 days (See Item 4) for a total of <u>7 measurements</u> (24, 48, 72, 96, 120, 144, and 168 hours).
Fentanyl	19813	3-Day PK Bioequivalence	1	72 hours	Daily measurements for 3 days (See Item 1) for a total of <u>3 measurements</u> (24, 48, and 72).
Granisetron	22198	7-Day PK Bioequivalence	1	168 hours (7 days)	Daily measurements for 7 days (See Item 4) for a total of <u>7 measurements</u> (24, 48, 72, 96, 120, 144, and 168 hours).
Lidocaine	20612	Guidance unclear			
Methylphenidate	21514	21-Day Induction Phase	9	48-72 hours	Only take measurements on the <i>first</i> patch (See Item 18). There does not seem to be any recommendation regarding the number of measurements other than 9 hours after application.
Nitroglycerin	74559	21-Day	21	24 hours	Only take measurements on the <i>first</i>

Table 1. Summary of Patch Adhesion Sampling Regimes for Bioequivalence Guidance Documents with a Transdermal/Topical Route of Administration

Active Ingredient	RLD	Study	Total No. of TEST Patches	Length of Wear/Patch	Sampling Regime/Patch
		Induction Phase			patch (See Item 2); <u>1 measurement</u> 24 hours after application.
Nitroglycerin	20145	1/2-Day PK Bioequivalence	1	12 hours	<u>One measurement</u> 12 hours after application (see Item 3).
Oxybutynin	21351	4-Day PK Bioequivalence	1	96 hours	Daily measurements for 4 days (See Item 2) for a total of <u>4 measurements</u> (24, 48, 72, and 96).
Rivastigmine	22083	1-Day PK Bioequivalence	1	24 hours	<u>One measurement</u> 24 hours after application (See Item 1).
Scopolamine	17874	3-Day PK Bioequivalence	1	72 hours	Daily measurements for 3 days (See Item 1) for a total of <u>3 measurements</u> (24, 48, and 72).
Selegilin	21336	21-Day Induction Phase	21	24 hours	Only take measurements on the <i>first</i> patch (See Item 2); <u>1 measurement</u> 24 hours after application.

In contrast to clinical trials which seek to show that a new drug product performs better than a comparator, non-inferiority (NI) trials are designed to determine whether the differences in treatment effect or product quality between a new drug product or generic equivalent and the comparator (RLD) are small and statistically non-significant, as discussed in the Agency’s draft guidance on NI clinical trials.¹ For patch adhesion, ensuring that the generic is non-inferior to the RLD requires that the instances of detachment in the generic fall below the adjusted level of detachments observed in the RLD during the length of wear. The design structure for an NI adhesion trial is a randomized complete block or a two-period crossover; in both types of studies the treatment structure is a one-way with two levels, test and RLD. Each subject wears both the test and RLD patch simultaneously or in sequence. The response variable is the mean adhesion score except in those cases where the duration of wear allows for only one adhesion measurement. Therefore the response variable can be a single measurement or the mean of three, four, or seven measurements. The mean can range from zero to four, but the number of possible outcomes increases with the number of measurements. For example, there are five possible outcomes for a single adhesion measurement and 35 possible outcomes when adhesion is measured 3 times.

Current Methodology for Establishing NI

The NI evaluation of the test product versus the RLD must demonstrate that the upper bound of a one-sided 95% confidence limit of the mean adhesion score for the test

¹ FDA Guidance for Industry – Draft Guidance on Non-Inferiority Clinical Trials. Last accessed on November 20, 2013 via <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM202140.pdf>

product minus 1.25 times the mean adhesion score for the RLD product is less than or equal to 0. The hypotheses are:

$$H_0: \mu_{\text{Test}} - 1.25\mu_{\text{RLD}} > 0 \quad \text{vs.} \quad H_a: \mu_{\text{Test}} - 1.25\mu_{\text{RLD}} \leq 0$$

where μ_{Test} is the least squares mean for the test product and μ_{RLD} is the least squares mean for the reference. If the 95% upper limit is less than or equal to zero, the null hypothesis is rejected and the test is considered NI to the RLD.

The null hypothesis is evaluated using a linear mixed model with “Treatment” as a fixed effect and “Subject” as a random effect. It is recommended the analysis be conducted in SAS[®] using the following code.

```
Proc Mixed Data = <dataset name>;  
Class Subject Treatment;  
Model MCA = Treatment / DDFM = Satterth;  
Repeated Treatment / sub = Subject type = fa0(2) r;  
Estimate 'Test - 1.25*Reference' int - 0.25 Treatment 1-1.25 / cl alpha = 0.1;  
LSMeans Treatment;  
Run;
```

Issues with the Approach

Past use of linear mixed model analysis has been appropriate for assessing NI with these types of products. However, as generic and RLD patch drug products have improved their adhesive performance, the appropriateness of the FDA recommended method for establishing NI has come under question. One of the key assumptions when using linear mixed models is that both the model parameters for the random effects portion and the residuals from the data follow a normal distribution (see Appendix I for details). With highly adhering products, adhesion scoring becomes dominated by zeros ($\geq 90\%$ attached), and in extreme cases, is entirely comprised of zeros. This results in data that are highly right skewed and thus non-normal. When using data from highly skewed distributions in a mixed model analysis where inferences are based on the t -distribution, it is not clear if the true coverage probability approximates the nominal coverage probability.

To get a better sense of the types of adhesion score distributions submitted to the FDA, adhesion scoring data from 15 ANDAs were used to determine the frequency of each score level (i.e. 0, 1, 2, 3, 4) in each adhesion study (see Appendix II and III for more details). The results are shown below in Table 2.

Table 2: Adhesion Score Frequency of Patch Drug Products and Their Ability to Pass FDA’s Recommended Non-Inferiority Analysis

Drug Products	ANDA	RLD	Number of Time Points	TEST %Score = 0	TEST %Score = 1	TEST %Score = 2	TEST %Score = 3	TEST %Score = 4	REFERENCE %Score = 0	REFERENCE %Score = 1	REFERENCE %Score = 2	REFERENCE %Score = 3	REFERENCE %Score = 4	Passed NI (Ran by Statistician)	Passed NI (Ran by Bryan Newman)
Norelgestromin/ Estradiol TDS	200910	21180	7	100.0%	0.0%	0.0%	0.0%	0.0%	99.6%	0.4%	0.0%	0.0%	0.0%	no	CNR*
(b) (4)															
Estradiol TDS	201675	20538	4	98.5%	1.1%	0.0%	0.1%	0.3%	98.8%	0.8%	0.1%	0.1%	0.2%	no	no
(b) (4)															
Lidocaine	200675	20612	7	91.4%	6.0%	2.0%	0.6%	0.0%	91.4%	6.0%	2.0%	0.6%	0.0%	yes	yes
Clonidine	76157	18891	7	86.1%	7.3%	1.4%	0.7%	4.5%	72.5%	18.6%	3.0%	1.8%	4.1%	yes	yes
(b) (4)															
Clonidine TDS	79090	18891	8	82.8%	13.6%	0.0%	0.8%	2.8%	92.0%	3.4%	0.8%	0.6%	3.2%	yes	yes
Fentanyl	202097	19813	7	77.0%	21.1%	1.9%	0.0%	0.0%	74.5%	25.5%	0.0%	0.0%	0.0%	no	no
Scopolamine	78830	17874	6	61.5%	31.6%	5.2%	1.7%	0.0%	59.2%	35.6%	2.9%	0.0%	2.3%	no	no
(b) (4)															
Lidocaine	202346	20612	6	34.7%	52.8%	11.8%	0.7%	0.0%	47.2%	29.9%	11.8%	3.5%	7.6%	yes	yes

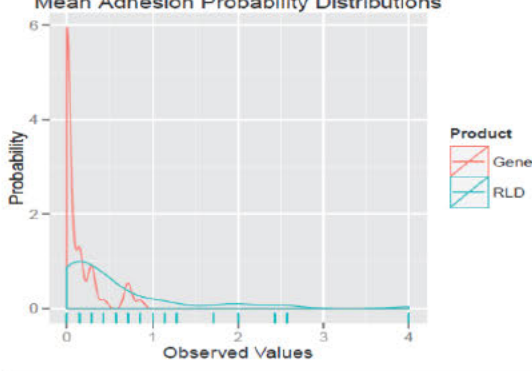
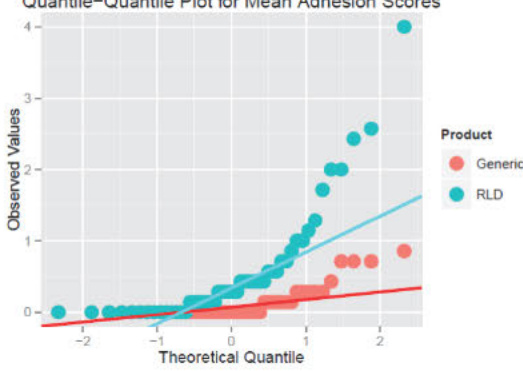
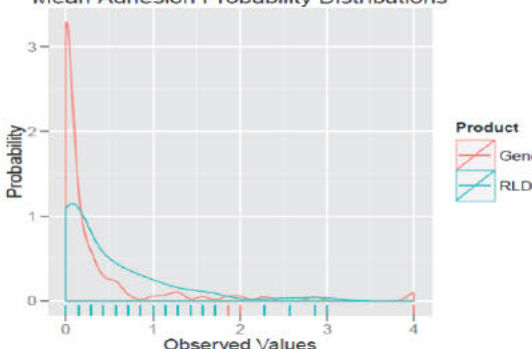
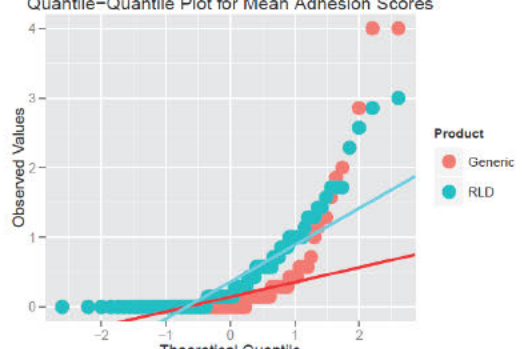
*** Convergence Not Reached**

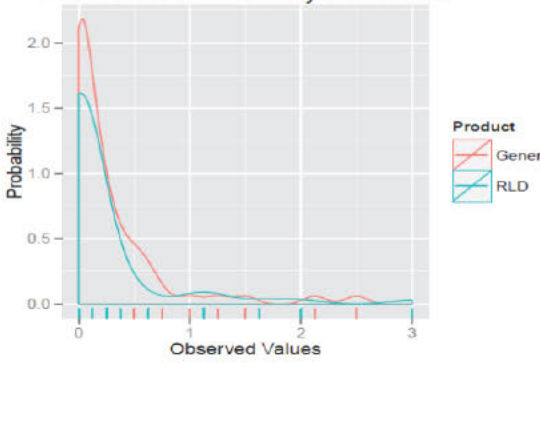
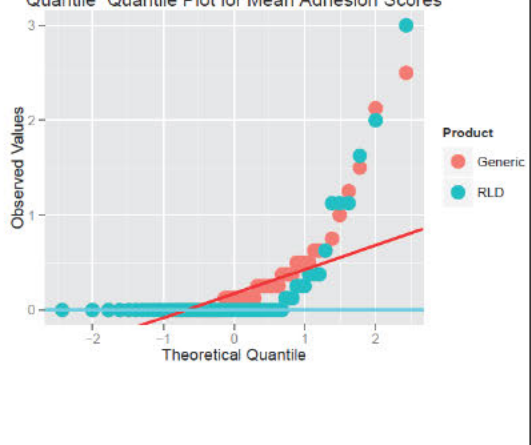
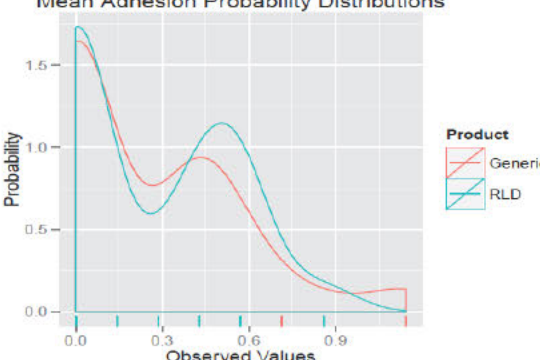
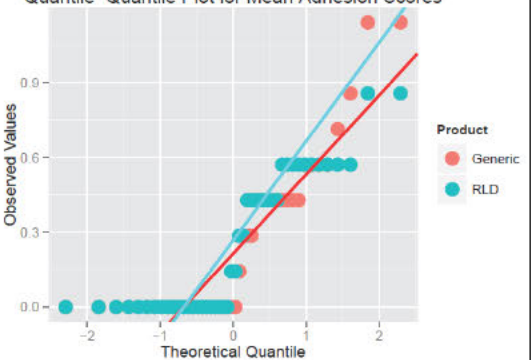
As shown in Table 2, adhesion scoring frequency varies considerably, with the highest adhering products Norelgestromin/Ethinyl Estradiol (ANDA 200910), (b) (4) (b) (4) Estradiol (ANDA 201675), (b) (4) (b) (4) and Lidocaine (ANDA 200675) having greater than 90% of the reported adhesion scores being zero. Importantly, when the adhesion scoring frequency for zero scores approached 100%, the mixed model analysis either failed to establish NI, or the SAS procedure failed to converge.

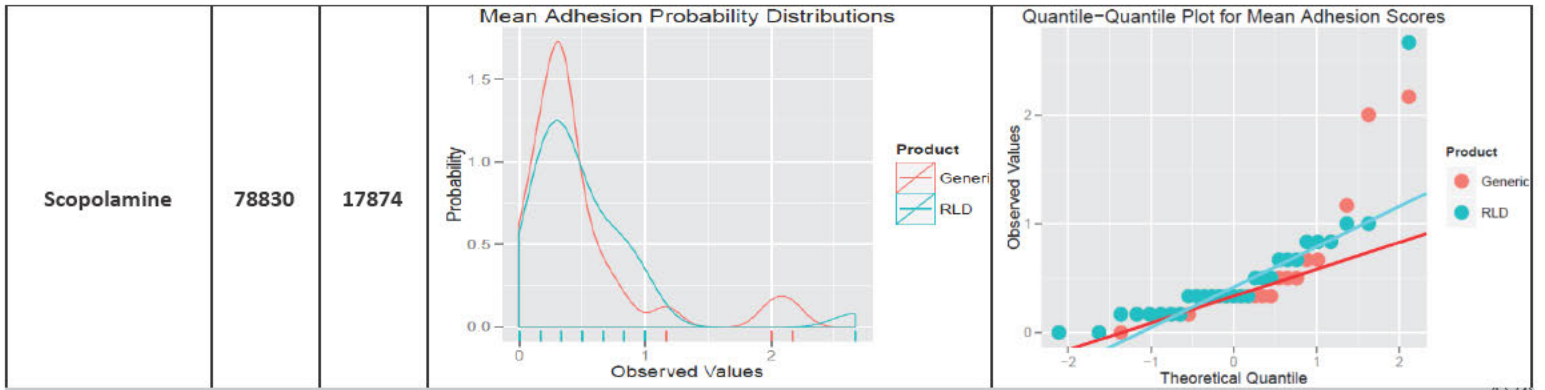
In addition to the adhesion score frequency, probability distributions and quantile-quantile plots were created for the mean adhesion score values from each of the 15 ANDAs (Table 3). While the normality of the mean adhesion values from many of the drug products is questionable (b) (4) (b) (4) the top 3 highly adhering products (98-100% zero scores) clearly deviate from what would be expected if the mean adhesion values were normally distributed.

Table 3: Comparison of the Mean Adhesion Probability Distributions and Quantile-Quantile Plots for the Top 5 Generic and Brand Patch Drug Products

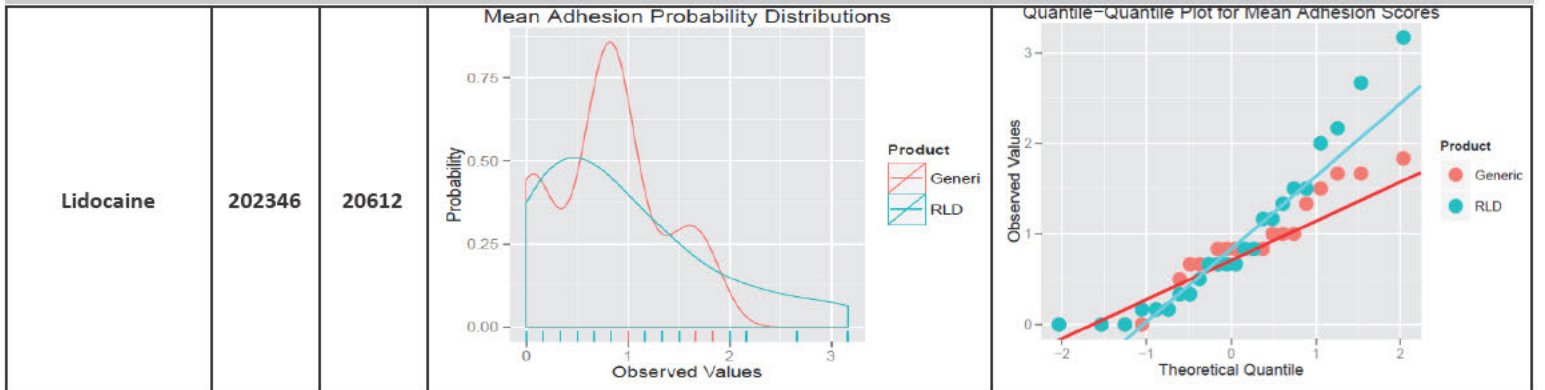
Drug Product	ANDA	RLD	Mean Adhesion Probability Distributions	Mean Adhesion Quantile-Quantile Plots
Norelgestromin/ Estradiol TDS	200910	21180		
Estradiol TDS	201675	20538		

Lidocaine	200675	20612		
Clonidine	76157	18891		

Clonidine TDS	79090	18891	Mean Adhesion Probability Distributions 	Quantile-Quantile Plot for Mean Adhesion Scores 
Fentanyl	202097	19813	Mean Adhesion Probability Distributions 	Quantile-Quantile Plot for Mean Adhesion Scores 



(b) (4)



It can be argued that, while using mixed model analysis is inappropriate when the distribution of mean adhesion values is non-normal, it is still possible for a generic product to pass NI testing if its level of adhesion is sufficiently better than the RLD being compared. As previously mentioned above, past innovator products often had worse adhesive properties compared to their generic counterparts, since generics would have access to current, more favorable adhesives that were not available to the innovator during product development. However, today's patch drug products often show highly adhering properties, leaving little room for generics to improve upon. Thus, a new methodology is required to handle highly adhering products where the extreme non-normal distribution of the mean adhesion values clearly invalidates using mixed model analysis to establish NI.

Identification of Criterion for Demonstrating High Adherence and Waiver for the Non-inferiority Statistical Test

Given that the current approval process for evaluating adhesion is not acceptable, a simple remedy for this problem would be to identify a criterion that the Agency would consider a measure of high adherence. Generic products that were found to either meet or exceed this criterion would be viewed as having a sufficiently high adhesion rate that the current FDA NI requirement could be waived.

In 2012, the EMA published their *Draft Guidance on Quality of Transdermal Patches*², which, in terms of adhesive product quality, states

In general, a mean adherence of greater than 90% should be expected and no instances of detachment should be seen. Poor adherence events should be investigated and possible causes and risk factors determined.

In order to determine whether “ $\geq 90\%$ adhesion” for a generic product is a sufficient condition to serve as the waiver criterion for high adherence, this condition must be interpreted under the current FDA scoring paradigm. Given that the FDA adhesion score of zero implies $\geq 90\%$ adhesion, verifying “ $\geq 90\%$ adhesion” for a given study could be accomplished by determining the percentage of patches having $\geq 90\%$ adhesion at each measurement event throughout the study and taking the average of these percentages. If the average percentage was $\geq 90\%$, the Agency would view this product as having displayed sufficiently high adherence and the NI statistical analysis could be waived.

To illustrate the procedure, this analysis was performed with ANDA 201675, an estradiol containing transdermal patch sponsored by Mylan. The RLD for this drug product is Novartis's Vivelle-Dot®, approved on January 8, 1999 for the treatment of menopause-related symptoms and prevention of post-menopausal osteoporosis.³ As seen previously

² EMA. Draft Guideline on Quality of Transdermal Patches. August 23, 2012. Last accessed December 16, 2013 via http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/09/WC500132404.pdf

³ Drugs@FDA Drug Label for Vivelle-Dot (Estradiol) Transdermal System. Last accessed December 16, 2013 via http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020538s028s029s030lbl.pdf

in Table 2, both Mylan’s product and the RLD are highly adhering, with zero score frequency close to 100%. When this approach is used to assess ANDA 201675, both the generic and RLD meet the claim of $\geq 90\%$ adhesion (Table 4).

Table 4. Waiver Analysis for Mylan’s Estradiol Patch (ANDA 201675) and the RLD

TEST (ANDA 201675)			REFERENCE (Vivelle-Dot®)			
	Percentage of Patches with Score = 0	Average Adhesion Across Time Points		Percentage of Patches with Score = 0	Average Adhesion Across Time Points	
T1	228 / 228	98.46%	T1	228 / 228	100.00%	
T2	227 / 228		99.56%	T2	228 / 228	100.00%
T3	224 / 228		98.25%	T3	227 / 228	99.56%
T4	219 / 228		96.05%	T4	218 / 228	95.61%
			98.79%			

This approach was applied to the remaining 14 ANDAs to further gauge how this method would assess a range of adhesion data. Of the 15 ANDAs, 5 were found to meet the criterion (see Figure 1 and Table 5). In addition to a criterion of $\geq 90\%$ of patches having $\geq 90\%$ adhesion (referred to as 90/90), lower percentages for the average percentage were included in the analysis (80/90 and 75/90).

Figure 1. Waiver Analysis for All 15 ANDAs and Their Respective RLD

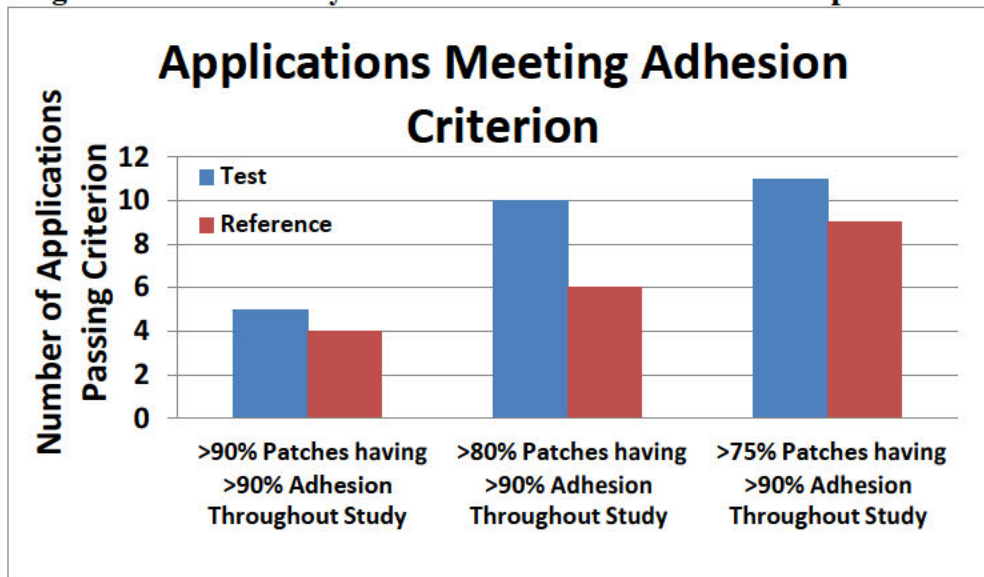


Table 5. Waiver Analysis for All 15 ANDAs and Their Respective RLD

ANDAs Passing 90/90 Criterion		Passed Non-Inferiority Testing		RLD	RLD Passed 90/90
		Ran by Statistician	Ran by B. Newman		
Norelgestromin/Estradiol TDS	200910	no	CNR*	21180	yes (b) (4)
Estradiol TDS	201675	no	no	20538	yes (b) (4)
Lidocaine	200675	yes	yes	20612	no
ANDAs Failing 90/90 Criterion		Ran by Statistician	Ran by B. Newman	RLD	RLD Passed 90/90
Clonidine	76157	yes	yes	18891	no (b) (4)
Clonidine TDS	79090	yes	yes	18891	no
Fentanyl	202097	no	no	19813	no
Scopolamine	78830	no	no	17874	no (b) (4)
Lidocaine	202346	yes	yes	20612	no

*CNR – Convergence Not Reached

ANDA 200910 (Norelgestromin/Ethinyl Estradiol TDS) was one of the 5 applications found to meet the 90/90 criterion. In the adhesion study that assessed NI between ANDA 200910 and the RLD, only a single adhesion score was nonzero (at one measurement event, the RLD had an adhesion score of 1). This is an extreme case where the adhesion profiles from both the generic and RLD display near perfect adhesion and mixed model analysis by the statistical reviewer found the generic inferior to the RLD. (b) (4)

It is also important to note that of the products failing to meet the 90/90 criterion, the majority passed the current FDA NI analysis.⁵ Given that many of the quantile-quantile plots for these products were questionable in their degree of normality, additional work is

⁵ In cases where the statistical review was not available for the ANDA, Bryan Newman performed the non-inferiority test using mixed model analysis with standard SAS code provided in most statistical reviews. Non-inferiority analysis was also done for ANDAs where the statistical review was complete to ensure accuracy of the method.

needed to understand these differences and develop a statistical method that is appropriate for all types of adhesion data.

Effect of Sample Size on Meeting Adhesion Criterion

In addition to identifying an acceptable adhesion criterion, it is also necessary to determine the minimum number of subjects that, will provide the agency with the confidence that the study size is adequate to determine whether the product meets the Agency's measure of high adhesion.

In order to determine an acceptable minimum sample size, adhesion data from each of the 15 ANDA applications were bootstrapped using random sampling of subjects with replacement to generate 5 sets of 10,000 bootstrap samples. In each set, a sample size was selected from the following list: 20, 36, 40, 60, and 80 subjects. Using these five bootstrapped sets, the number of studies meeting the adhesion criterion was tabulated to observe the effects of sample size on passing the criterion. If the adhesion study data submitted with the original product application failed the waiver criterion, than any study from the bootstrap data that passed the criterion can be viewed as a false positive. Therefore, the minimum sample size should be the number that keeps the false positive rate below a defined limit (i.e. 10%). Results for products originally found to fail the 90/90 waiver criterion are shown in Figure 4 and Figure 5 below.

Figure 4. Effect of Sample Size on Percentage of Studies Passing for ANDAs that Originally Failed the 90/90 Adhesion Criterion Waiver



Figure 5. Effect of Sample Size on Percentage of Studies Passing for RLDs that Originally Failed the 90/90 Adhesion Criterion Waiver



Results for several of the applications showed that, regardless of the bootstrap sample size the adhesion scores were too high (indicating poor adhesion) to produce a passing study. The effect of sample size was more apparent for products whose original analyses were close to the waiver criterion. For Clonidine 076157, the test product showed 86% of patches had $\geq 90\%$ adhesion for 90% of the study duration. As seen in the bootstrap analysis, decreasing the number of subjects in the study increased the percentage of passing studies (i.e. increasing the false positive rate). Studies consisting of 20 subjects showed a passing rate of slightly more than 25%. However, when 60 subjects were used the false positive rate fell below 10%. (b) (4)



his decision would be left for the clinical reviewer. In conclusion, these results demonstrate that adhesion studies consisting of at least 60 subjects provide sufficient data

to determine whether high adhesion has been demonstrated and the statistical NI analysis can be waived.

Summary

Highly adhering patch drug products that meet or exceed the adhesion criterion of 90/90 ($\geq 90\%$ of patches having $\geq 90\%$ adhesion throughout the entire study) should be permitted to waive the requirement of passing the NI statistical test, since meeting or exceeding these conditions is sufficient evidence for demonstrating high adhesion.

Additionally, for products to qualify for the adhesion statistical waiver, it is recommended that the adhesion studies contain a minimum of 60 subjects. This minimum subject number should provide the Agency with the confidence that the adhesion study is large enough to adequately determine whether a product meets the measure of high product quality. Lastly, it is important to note that the minimum sample size is solely for the qualification of the adhesion waiver, and not for studies using the FDA recommended method for establishing NI.

Reviewed By:

Bryan Newman, Ph.D.
Office of Generic Drugs, Science Staff
Center of Drug Research and Evaluation

Date

Concurrence:

Robert Lionberger, Ph.D.
Acting Deputy Director for Science
Office of Generic Drugs
Center of Drug Research and Evaluation

Date

APPENDIX

Appendix I: Details Regarding Linear Mixed Model Analysis and Assumptions

Application of a test and reference patch in an adhesion NI trial occurs simultaneously for each subject, with each subject's adhesion scores likely correlated. To handle these potential correlations, linear mixed model analysis is performed. An example of a linear mixed model is shown below in matrix notation:

$$Y = X\beta + Z\gamma + \varepsilon$$

where Y is the vector of observations, X and Z are the design matrices for the fixed and random variables respectively, β is the vector of fixed effects parameters, γ is the vector of random effects parameters, and ε is the vector of the residuals.^{6,7,8} The random effects portion of the mixed model is assumed to both assess and reflect the subject related correlations, while effects from the different treatments are handled in the fixed effects portion.

One of the key assumptions when using linear mixed models is that the random effects parameters γ and residuals ε from the data follow a normal (Gaussian) distribution with

$$E \begin{bmatrix} \gamma \\ \varepsilon \end{bmatrix} = \begin{bmatrix} \mathbf{0} \\ \mathbf{0} \end{bmatrix}$$
$$\text{Var} \begin{bmatrix} \gamma \\ \varepsilon \end{bmatrix} = \begin{bmatrix} \mathbf{G} & \mathbf{0} \\ \mathbf{0} & \mathbf{R} \end{bmatrix}$$

where G and R are the covariance matrices for the random effects parameters and residuals, respectively.⁹ In order for the model to provide estimates for the fixed and random parameters, G and / or R must be estimated. Given a normally distributed γ and ε , a likelihood-based approach, such as the restricted maximum likelihood (REML) method, can be used to estimate G and R.^{10,11,12,13,14}

⁶ Henderson, CR. Statistical Method in Animal Improvement: Historical Overview. *Advances in Statistical Methods for Genetic Improvement Livestock*. 1990; 1-14, New York: Springer-Verlag.

⁷ Searle, SR, Casella, G, McCulloch, CE. Variance Components. 1992: Wiley, New York.

⁸ SAS 9.2 User's Guide – Second Edition. Mixed Model Theory. Last accessed December 16, 2013 via http://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer.htm#statug_mixed_sect02_2.htm

⁹ SAS 9.2 User's Guide – Second Edition. Mixed Model Theory. Last accessed December 16, 2013 via http://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer.htm#statug_mixed_sect02_2.htm

¹⁰ Harley, HO., Rao, JNK. Maximum likelihood estimation for the mixed analysis of variance model. *Biometrika*. 1967; 54: 93-108

¹¹ Patterson, HD., Thompson, R. Recovery of inter-block information when block sizes are unequal. *Biometrika*. 1971; 58:545-554

¹² Harville, DA. Maximum-likelihood approaches to variance component estimation and to related problems. *J Amer Statist Assoc*. 1977; 72:320-340

¹³ Laird, NM., Ware, JH. Random-effects models of longitudinal data. *Biometrics*. 1982; 38(4):963-74

¹⁴ Jennrich, RI., Schluchter, MD. Unbalanced repeated-measures models with structured covariance matrices. *Biometrics*. 1986; 42(4):805-820

Appendix II: ANDA Data Set

ANDA		RLD Reference	Source of Adhesion Data	File Name
Clonidine	076157	18891	Study 160-0609-01	Ad2.xpt
Clonidine	079090	18891	Study 10616246	Crosstab.xpt
(b) (4)				
Estradiol	201675	20538	Study EDOT-0908	0908adhes.xpt
Fentanyl	202097	19813	Study S09-0330	Adh.xpt
(b) (4)				
Lidocaine	200675	20612	Study R09-0723	A73.xpt
Lidocaine	202346	20612	Study Lido-1044	1044rawadhes.xpt
(b) (4)				
Norelgestromin/Estradiol	200910	21180	Study ORTH-09198	09198adadhes.xpt
(b) (4)				
Scopolamine	078830	17874	Study PRG-604	Adh31201.xpt

*Adhesion score frequency tabulated in Table 2 (pg. 6) used data from files listed above

Appendix III: Frequency Data for each ANDA

* Frequency data used in calculation of average percent adhesion used for 90/90 determination was taken from charts found in study reports or statistics reviews (if available)

Clonidine	076157	18891	Study 160-0609-01	Ad2.xpt

Appendix B. Frequency table of Daily Adhesion Scores per Patch:

Adhesion Score Evaluation Day		Score					Total Subjects with Score	
		0	1	2	3	4	Greater Or Equal 3	Equal 4
Day 2	Test	98	8	0	0	2	2	2
	Reference	93	14	1	0	0	0	0
Day 3	Test	98	6	1	1	2	3	2
	Reference	80	24	4	0	0	0	0
Day 4	Test	98	7	0	0	3	3	3
	Reference	73	31	3	0	1	1	1
Day 5	Test	93	9	2	0	4	4	4
	Reference	79	20	3	3	3	6	3
Day 6	Test	93	9	0	0	6	6	6
	Reference	75	23	3	2	5	7	5
Day 7	Test	85	11	2	2	8	10	8
	Reference	74	16	4	8	6	14	6
Day 8	Test	90	4	5	1	8	9	8
	Reference	76	11	5	1	15	16	15

A = Test Clonidine Patch

B = Test Overlay

C = Reference Clonidine Patch

D = Reference Overlay

TRT	dy1ADH	Total
Frequency	100	
Row Pet		
A	68 100.00	68
B	68 100.00	68
C	68 100.00	68
D	68 100.00	68
Total	272	272

TRT	dy2ADH	Total			
Frequency	75	85	95	100	
Row Pet					
A	0 0.00	0 0.00	4 5.97	63 94.03	67
B	1 1.49	0 0.00	2 2.99	64 95.52	67
C	0 0.00	1 1.49	4 5.97	62 92.54	67
D	0 0.00	1 1.49	2 2.99	64 95.52	67
Total	1	2	12	253	268

Frequency Missing = 4

TRT	dy3ADH	Total			
Frequency	0	85	95	100	
Row Pet					
A	0 0.00	0 0.00	9 13.B	58 86.57	67
B	1 1.49	1 1.49	1 1.9	64 95.52	67
C	2 2.99	2 2.99	9 13.B	54 80.60	67
D	1 1.49	1 1.49	0 0.00	65 97.01	67
Total	4	4	19	241	268

Frequency Missing = 4

TRT dy4ADH

Frequency Row Pct	0	75	85	95	100	Total
A	1 1.49	1 1.49	6 8.96	31 46.27	28 41.79	67
B	0 0.00	0 0.00	0 0.00	1 1.52	65 98.48	66
C	1 1.54	2 3.08	5 7.69	31 47.69	26 40.00	65
D	0 0.00	0 0.00	1 1.52	0 0.00	65 98.48	66
Total	2	3	12	63	184	264

Frequency Missing = 8

TRT dy5ADH

Frequency Row Pct	0	65	75	85	95	100	Total
A	1 1.54	0 0.00	2 3.08	9 13.85	38 58.46	15 23.08	65
B	1 1.54	2 3.08	0 0.00	1 1.54	0 0.00	61 93.85	65
C	1 1.59	0 0.00	2 3.17	12 19.05	39 61.90	9 14.29	63
D	2 3.08	0 0.00	0 0.00	1 1.54	1 1.54	61 93.85	65
Total	5	2	4	23	78	146	258

Frequency Missing = 14

TRT dy6ADH

Frequency Row Pet	0	35	45	55	75	85	95	100	Total
A	1 1.56	0 0.00	1 1.56	0 0.00	1 1.56	B 12.50	28 43.75	25 39.06	64
B	1 1.56	0 0.00	0 0.00	1 1.56	1 1.56	4 6.25	10 15.63	47 73.44	64
C	0 0.00	0 0.00	0 0.00	1 1.61	4 6.45	11 17.74	30 48.39	16 25.81	62
D	2 3.13	1 1.56	0 0.00	0 0.00	0 0.00	0 0.00	7 10.94	54 84.38	64
Total	4	1	1	2	6	23	75	142	254

Frequency Missing 18

TRT dyADH

Frequency Row Pet	0	15	25	35	45	75	85	95	D0	Total
A	- n.n	0 n.on	0 n nn	0 o .nn	1 1.h1	1 .61	16 24.2	12 18.1	31 46.6	62
B	- 1.6	1 1.61	0 0.00	1 1.61	0 0.00	1 1.61	4 6.08	12 18.1	42 64.0	52
C	3 4.92	0 0.00	1 1.64	0 0.00	1 1.64	4 6.56	16 26.23	10 15.39	25 42.62	51
D	- 1.6	0 0.00	0 0.00	0 0.00	0 0.00	2 3.2	3 4.84	10 15.13	45 74.8	52
Total	6	1	1	1	2	0	3)		HS	247

Frequency Missing 25

TRT dy8ADH

Frequency Row Pct	0	5	25	45	55	75	85	95	100	Total
A	1 1.61	0 0.00	0 0.00	2 3.23	0 0.00	5 8.06	23 37.10	21 33.87	10 16.13	62
B	3 4.76	0 0.00	1 1.59	0 0.00	1 1.59	2 3.17	5 7.94	16 25.40	35 55.56	63
C	2 3.39	1 1.69	0 0.00	1 1.69	2 3.39	6 10.17	27 45.76	18 30.51	2 3.39	59
D	1 1.59	0 0.00	0 0.00	0 0.00	0 0.00	1 1.59	6 9.52	17 26.98	38 60.32	63
Total	7	1	1	3	3	14	61	72	85	247

Frequency Missing = 25



(b) (4)



(b) (4)

Estradiol	201675	20538	Study EDOT-0908	0908adhes.xpt

Table 2: Frequency of adhesion scores (ADHPP)

Visit	Treatment	Adhesion score				
		0	1	2	3	4
2	Test	228	0	0	0	0
	Reference	228	0	0	0	0
3	Test	227	1	0	0	0
	Reference	228	0	0	0	0
4	Test	224	4	0	0	0
	Reference	227	1	0	0	0
5	Test	219	5	0	1	3
	Reference	218	6	1	1	2

Fentanyl	202097	19813	Study S09-0330	Adh.xpt

Table 12: Frequency of adhesion scores

Evaluation hours	Treatment	Adhesion score		
		0	1	2
0	Test	46		
	Reference	46		
12	Test	45	1	
	Reference	44	2	
24	Test	42	4	
	Reference	44	2	
36	Test	38	8	
	Reference	33	13	
48	Test	28	16	2
	Reference	27	19	
60	Test	25	19	2
	Reference	23	23	
72	Test	24	20	2
	Reference	23	23	

Lidocaine	200675	20612	Study R09-0723	A73.xpt

Number (Percent) of Subjects for Evaluated Adhesion Score at Each Time Point (per sponsor)

Treatment	Score	Hour 0	Hour 2	Hour 4	Hour 6	Hour 8	Hour 10	Hour 12
A	0	50(100%)	50(100%)	50(100%)	50(100%)	47(94%)	38(76%)	35(70%)
A	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (6%)	8 (16%)	10 (20%)
A	2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (8%)	3 (6%)
A	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (4%)
A	4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
B	0	49 (98%)	49 (98%)	46 (92%)	39 (78%)	27(54%)	18(36%)	19(38%)
B	1	0 (0%)	0 (0%)	2 (4%)	6 (12%)	14(28%)	18(36%)	18(36%)
B	2	0 (0%)	0 (0%)	1 (2%)	2 (4%)	2 (4%)	6 (12%)	3 (6%)
B	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (6%)	2 (4%)	3 (6%)
B	4	1 (2%)	1 (2%)	1 (2%)	3 (6%)	4 (8%)	6 (12%)	7 (14%)

Treatment A: test

Treatment B: reference

Lidocaine	202346	20612	Study Lido-1044	1044rawadhes.xpt

Table 11: Frequency of adhesion scores (ADHFPP)

Evaluation hours	Treatment	Adhesion score	0	1	2	3	4
2	Test	16	8				
	Reference	23	1				
4	Test	11	12	1			
	Reference	19	4		1		
6	Test	9	12	3			
	Reference	9	11	2		2	
8	Test	15	7	2			
	Reference	10	6	4	2	2	
10	Test	14	7	3			
	Reference	7	8	5	1	3	
12	Test	12	10	1	1		
	Reference	4	9	6	1	4	

Norelgestromin/Estradiol	200910	21180	Study ORTH-09198	09198adadhes.xpt

Adhesion Scores							
Hours	Adhesion Score		Score				
	Evaluation Day		0	1	2	3	4
24	Day 2	Test	38				
		Reference	38				
48	Day 3	Test	38				
		Reference	38				
72	Day 4	Test	38				
		Reference	38				
96	Day 5	Test	38	0			
		Reference *	37	1			
120	Day 6	Test	38				
		Reference	38				
144	Day 7	Test	38				
		Reference	38				
168	Day 8	Test	38				
		Reference	38				

*: Subject No 18 in the Reference product at visit 96 Hours

Scopolamine	078830	17874	Study PRG-604	Adh31201.xpt

Table 11: Frequency of adhesion scores

Evaluation hours	Treatment	Adhesion score				
		0	1	2	3	4
12	Test	22	6		1	
	Reference	25	5			
24	Test	12	15	2		
	Reference	14	16			
36	Test	24	2	3		
	Reference	24	5			1
48	Test	18	9	2		
	Reference	12	15	2		1
60	Test	24	4		1	
	Reference	24	4	1		1*
72	Test	7	19	2	1	
	Reference	9	18	2		1*

*: Subjects, #3 reference patch fell off after Hour 48. A score 4 at Hour 48 was carried forward to Hour 60 and 72.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAIVA SHETTY
06/11/2014

JOHN R PETERS
06/18/2014

ETHAN M STIER
06/18/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 204403

CHEMISTRY REVIEWS

Recommendation:

ANDA:

Approval with Post-Marketing Commitments

Information Request

(_____ days for applicant to response)

Complete Response - Minor

Complete Response – Major

ANDA 204403

Amendment Review

Drug Name/Dosage Form	Rivastigmine Transdermal System
Strength	4.6 mg/ 24 hours (5 cm ²) 9.5 mg/ 24 hours (10 cm ²) 13.3 mg/ 24 hours (15 cm ²)
Reviewer(s)	Suneela Prodduturi
Applicant	Alvogen Pine Brook, Inc.

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
SD27 (eCTD 27) Quality/Response to IR	06/17/2015
SD26 (eCTD 26) Quality/Response to IR	06/16/2015
SD25 (eCTD 25) Quality/Response to IR	05/14/2015
SD19 (eCTD 19) Quality/Response to IR	10/10/2014
SD17 (eCTD 17) Quality/Response to IR	10/02/2014
SD13 (eCTD 13) Quality/Response to IR	09/20/2013
SD08 (eCTD 08) Quality/Response to IR	04/22/2013
SD05 (eCTD 03) Quality/Response to IR	01/22/2013
SD02 (eCTD 02) Quality/Response to IR	01/03/2013
SD00 (eCTD 00) New ANDA	06/12/2012

DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ²	Date Review Completed	COMMENTS
(b) (4)	II	(b) (4)	Rivastigmine (API)	Adequate	04/17/2015	Reviewed by Anita Tiwari
	IV	(b) (4)	(b) (4)	Adequate	05/15/2015	reviewed by S. Prodduturi
	IV	(b) (4)	(b) (4)	Adequate	05/15/2015	reviewed by S. Prodduturi
	IV	(b) (4)	(b) (4)	Adequate	06/23/2015	reviewed by S. Prodduturi
	III	(b) (4)	(b) (4)	N/A		
	III	(b) (4)	(b) (4)	N/A		
	III	(b) (4)	(b) (4)	N/A		

¹ Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Clinical (For levels of (b) (4) in the (b) (4) adhesive)	DCR	Adequate	06/16/2015	Melanie Mueller

FACILITIES:

Overall Recommendation: Acceptable			
Drug Substance			
Function	Site Information	FEI#	Status
Drug Substance Manufacture, Micronization, Sterilization or Testing Sites	(b) (4)	(b) (4)	(b) (4)
Drug Product			
Function	Site Information	FEI #	Status

*Drug Product
Manufacture,
Sterilization, Packaging,
Labeling or Testing Sites*

(b) (4)

2.3.S DRUG SUBSTANCE

1. The drug master file (b) (4) has been reviewed, as amended, and found inadequate. The DMF holder, (b) (4), was notified of any deficiencies on May 12, 2014. Please do not respond to this letter until the DMF holder has notified you that they have amended the DMF with their response.

The DMF holder, (b) (4), submitted a response to the Agency's comment letter of May 12, 2014 and addressed all deficiencies pertaining to DMF # (b) (4) on August 1, 2014. A copy of the transmittal letter is provided in Module 1.2.

Reviewer's Comment (Review # 2): Adequate

The DMF review dated 04/17/2015 indicates that DMF is adequate. There were no changes in the drug substance section including the specifications.

(b) (4)

Overall Reviewer's Assessment and Signature:

Adequate Suneela Prodduturi, 04/17/2015, 06/23/2015

Secondary Review Comments and Concurrence: Adequate with PMCs

Robert T. Berendt, 06/24/2015

Post-marketing commitments:

FDA references ANDA 204403/sequence 0027 submitted on 06/17/2015 and has the following comments:

1) FDA agrees that the Rivastigmine Transdermal Systems which have already been produced in anticipation of launch, specifically Batch Numbers P0016AL0AT, P0018AL0AT, P0004AL0AU, P0006AL0AU, P0008AL0AU, P0010AL0AU, P0012AL0AU, P0014AL0AU, P0022AL0AU, P0024AL0AU, P0026AL0BC, P0028AL0BC, P0028AL1BC, P0030AL0BC, P0032AL0BC, and P0034AL0BC with backing membrane printed "as is" may be released to the market upon Final Approval of the application from FDA.

2) FDA agrees with Alvogen commitment to printing the backing membrane with full product name and strength on all future produced batches of Rivastigmine Transdermal Systems as shown in the mock-up layouts provided in Module 1.2.

3) FDA agrees with Alvogen commitment to submitting the change described in Number 2 and the documentation associated with the change as a CBE-30 Changes Being Effected Supplement on the day of Final Approval.

Not Approvable – Major Deficiencies

ANDA 204403

Rivastigmine Transdermal System

4.6 mg/ 24 hours (b) (4)
9.5 mg/ 24 hours
13.3 mg/ 24 hours

Alvogen Pine Brook, Inc.

CR#1

Expedited Review

**Norman E. Ohler
Chemistry Division I**

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5. PREVIOUS DOCUMENTS:	1
6. SUBMISSION(S) BEING REVIEWED:	1
7. NAME & ADDRESS OF APPLICANT:	1
8. DRUG PRODUCT NAME/CODE/TYPE:	2
9. LEGAL BASIS FOR SUBMISSION: 505 (j)	2
10. PHARMACOL. CATEGORY: Treatment of Alzheimer’s disease and Parkinson’s disease dementia	2
11. DOSAGE FORM: Film, Transdermal Patch	2
12. STRENGTH/POTENCY:	2
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Chemistry Review Data Sheet

1. ANDA: 204403

2. REVIEW #: 1

3. REVIEW DATE: 12/09/2013

4. REVIEWER: Norman E. Ohler

5. PREVIOUS DOCUMENTS:

<u>Previous Document(s)</u>	<u>Document Date</u>
None	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
SD13 (eCTD 13) Quality/Response to IR	09/20/2013
SD08 (eCTD 08) Quality/Response to IR	04/22/2013
SD05 (eCTD 03) Quality/Response to IR	01/22/2013
SD02 (eCTD 02) Quality/Response to IR	01/03/2013
SD00 (eCTD 00) New ANDA	06/12/2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Alvogen Pine Brook, Inc.
Address:	10 Bloomfield Avenue Building B Pine Brook, NJ 07058
Representative:	Jasmine Shah – VP, Regulatory and Medical Affairs
Telephone:	(b) (6)

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: None

Non-Proprietary Name (USAN): Rivastigmine Transdermal System

9. LEGAL BASIS FOR SUBMISSION: 505 (j)

Innovator Product: Exelon® Patch (rivastigmine transdermal system)

Innovator Company: Novartis Pharmaceutical Corporation

NDA: 22083

Patent Certifications for 4.6 mg/ 24 hours and 9.5 mg/ 24 hours:

Patent No.	Patent Expiration
4948807	Aug 14, 2012 (Drug substance)
5602176	Feb 11, 2014 (Drug substance)
6316023	Jan 8, 2019
6335031	Jan 8, 2019

Exclusivity Data for 4.6 mg/ 24 hours and 9.5 mg/ 24 hours:

There is no unexpired exclusivity for these products.

Patent Certifications for 13.3 mg/ 24 hours:

Patent No.	Patent Expiration
5602176	Feb 11, 2014 (Drug substance)
6316023	Jan 8, 2019
6335031	Jan 8, 2019

Exclusivity Data for 13.3 mg/ 24 hours:

Exclusivity Code	Exclusivity Expiration
NPP	Jun 27, 2016
NS	Aug 31, 2015

10. PHARMACOL. CATEGORY: Treatment of Alzheimer’s disease and Parkinson’s disease dementia

11. DOSAGE FORM: Film, Transdermal Patch

12. STRENGTH/POTENCY:

4.6 mg/ 24 hours (b) (4)

9.5 mg/ 24 hours (b) (4)

13.3 mg/ 24 hours (b) (4)

13. ROUTE OF ADMINISTRATION: Transdermal**14. Rx/OTC DISPENSED:** Rx OTC**15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):** SPOTS product – Form Completed Not a SPOTS product**15b. NANOTECHNOLOGY PRODUCT TRACKING:** NANO product – Form Completed (See Appendix A.4) Not a NANO product**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Chemical Names: (S)-3-[1-(Dimethylamino)ethyl] phenyl ethylmethylcarbamate

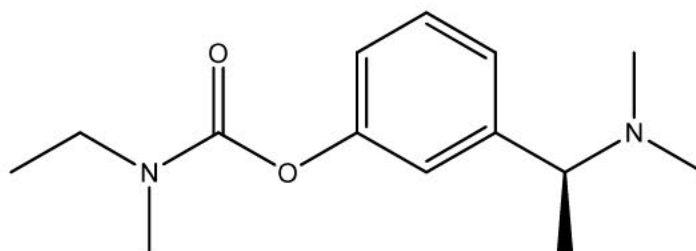
ChemBioDraw name: (S)-3-(1-(dimethylamino)ethyl)phenyl ethyl(methyl)carbamate

Molecular Weights: 250.34

Molecular Formula: C₁₄H₂₂N₂O₂

CAS#: 123441-03-2

Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	Date Review Completed	COMMENTS
(b) (4)	II	(b) (4)	Rivastigmine (API)	1	Inadequate	Currently under review	DMF team
	IV	(b) (4)	(b) (4)	1	New DMF	Currently under review	reviewed by N.E. Ohler
	IV	(b) (4)	(b) (4)	1	New DMF	Currently under review	reviewed by N.E. Ohler
	IV	(b) (4)	(b) (4)	1	review vol 11	Currently under review	reviewed by N.E. Ohler
	III	(b) (4)	(b) (4)	4	N/A		
	III	(b) (4)	(b) (4)	4	N/A		
	III	(b) (4)	(b) (4)	4	N/A		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
Methods Validation	N/A		
Labeling	Inadequate	09/24/2013	Barlow, James T
Bioequivalence	Inadequate (Dissolution)	09/24/2013	Raofi, Saeid
Toxicology/Clinical	N/A		
EA	Exception granted	11/09/2013	N.E. Ohler
Radiopharmaceutical	N/A		
Samples Requested	Yes		
EES Report	Overall Pending	26-SEP-2012	

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

Expedited in DARRTS

20. EES INFORMATION

Drug Substance			
Function	Site Information	FEI/CFN#	Status
Manufacturer		(b) (4)	OAI Status: NONE
Drug Product			
Function	Site Information	FEI/CFN#	Status
Finished Product Manufacturing, Packaging and Testing Facility		(b) (4)	OAI Status: NONE

Chemistry Review Data Sheet

	(b) (4)		
Contract Testing Laboratory: (Microbiological testing of the finished product)	(b) (4)		

Chemistry Review for ANDA 204403

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable.

CMC has major deficiencies.

Bioequivalence and labeling have been found inadequate.

EES was found overall Pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not approvable no recommendations at this time.

II. Summary of Chemistry Assessments

(b) (4)

Executive Summary Section

(b) (4)

**A. Description of the Drug Product(s) and Drug Substance(s)****Drug Substance:**

Rivastigmine is the free base of rivastigmine hydrogen tartrate, which is the active in the approved product Exelon[®] capsules and oral solution (b) (4) and 21-025, respectively). While the hydrogen tartrate exists as crystalline solid, the free base is a clear, slightly brown colored viscous liquid. The drug substance is being manufactured by (b) (4)

Drug Product:

The drug product, Rivastigmine Transdermal Delivery Patch, is a once a day treatment for the dementia of the Alzheimer's disease and for the treatment of dementia in patients with Parkinson's disease. Rivastigmine transdermal system (Rivastigmine-TDS) is a matrix patch consisting of two matrix layers. It is available in three strengths 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr. The compositions of all strengths are the same and the only difference is the patch size. The patches are a circular shape.

(b) (4)



Executive Summary Section

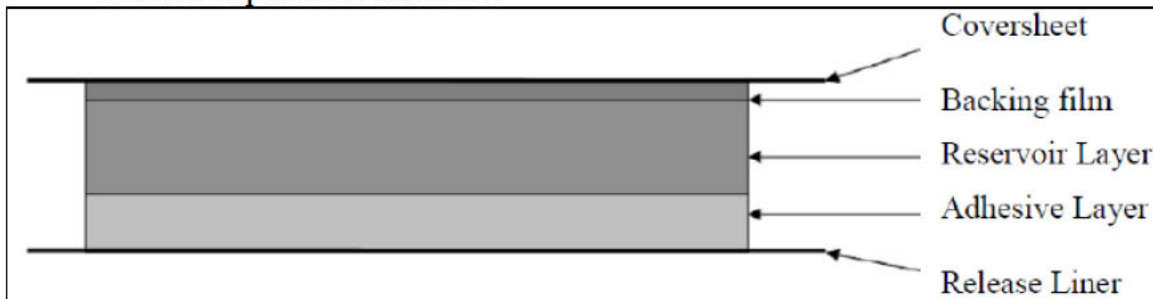
polyisobutenes is used in the adhesive matrix. An (b) (4) backing liner made from aluminum coated polyester combined with (b) (4) polyethylene has been chosen to protect the patch from the environment. The patch is situated on a standard release liner with fluoropolymer-coating.

After manufacturing each transdermal patch, together with a cover sheet made of polyethylene terephthalate siliconized on one side, (b) (4)

(b) (4)

(b) (4)

Scheme of patch shown below:

**B. Description of How the Drug Product is Intended to be Used**

The drug product is being developed for treatment of Alzheimer disease. This dosage form allows for once-a-day administration and useful in patients that are reluctant to be compliant.

Rivastigmine transdermal system should be applied once a day to clean, dry, hairless, intact healthy skin in a place that will not be rubbed against by tight clothing. The upper or lower back is recommended as the site of application because the patch is less likely to be removed by the patient; however, when sites on the back are not accessible the patch can be applied to the upper arm or chest. The patch should not be applied to skin that is red, irritated, or cut. It is recommended that the site of patch application be changed daily to avoid potential irritation, although consecutive patches can be applied to the same anatomic site (e.g., another spot on the upper back).

The patch should be pressed down firmly until the edges stick well. The patch can be used in situations that include bathing (b) (4)

Basis for Approvability or Not-Approval Recommendation

ANDA 204403 is not Approvable from a chemistry standpoint. The applicant is using a backing film that contains aluminum and may leave the user susceptible to burns during an MRI procedure. More information is required regarding controls of excipients and the use of a new adhesive will require more information so a tox consult can be requested. The API is undergoing oxidation degradation in the drug product. Bioequivalence and labeling have been found inadequate. EES is overall pending.

Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2

2.3 Introduction to the Quality Overall Summary

<i>Proprietary Name of Drug Product</i>	N/A
<i>Non-Proprietary Name of Drug Product</i>	Rivastigmine Transdermal
<i>Non-Proprietary Name of Drug Substance</i>	Rivastigmine
<i>Company Name</i>	Alvogen Pine Brook, Inc.
<i>Dosage Form</i>	Transdermal Patch
<i>Strength(s)</i>	4.6 mg/ 24 hrs; 9.5 mg/ 24 hrs; 13.3 mg/ 24 hrs
<i>Route of Administration</i>	Transdermal
<i>Proposed Indication(s)</i>	Treatment of Alzheimer's disease and Parkinson's disease dementia

(b) (4)

A APPENDICES

A.1 Facilities and Equipment (biotech only)

N/A

A.2 Adventitious Agents Safety Evaluation

None

A.3 Novel Excipients

None

A.4 Nanotechnology Product Information

Not a nanotech product

Office of Pharmaceutical Science MAPP 5015.9, Attachment A:

1) This review contains new information added to the table below: Yes ☐ No ☒ Review date: _____
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes ☐; No ☐; Maybe (please specify): _____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____
3 b) What is the source of the nanomaterial? _____
4) Is the nanomaterial a reformulation of a previously approved product? Yes ☐ No ☐
5) What is the nanomaterial functionality? Carrier _____; Excipient _____; Packaging _____ API _____; Other _____
6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment? Soluble _____; Insoluble _____
7) Was particle size or size range of the nanomaterial included in the application? Yes ☐ (Complete 8); No ☐ (go to 9).

8) What is the reported particle size?

Mean particle size _____ ; Size range distribution _____ ;

Other _____

9) Please indicate the reason(s) why the particle size or size range was not provided:

10) What other properties of the nanoparticle were reported in the application (See Attachment E)?

11) List all methods used to characterize the nanomaterial?

R REGIONAL INFORMATION

R.1 Executed Batch Records
Provided in Section 3.2.R

R.2 Comparability Protocols
N/A

R.3 Methods Validation Package
Provided in Section 3.2.R

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Documents

Patent Certification:

Provided in section 1.3.5.2

Exclusivity:

Provided in section 1.3.5.3

Debarment Certification:

Provided in section 1.3.3

cGMP Statement:

Statement is provided in section 3.2.S.2.1 for the drug substance manufacturer. Statements are provided in section 3.2.P.3.1 for the drug product manufacturer and related facilities.

Reprocessing Statement:

Provided in section 3.2.P.3.3

Letters of Authorization:

Provided in section 1.4.1

Request for Bio-waiver:

Provided in section 1.12.15

Citizen Petition and/or Control Request Linked to the Application:

None found

Environmental Impact Considerations/Categorical Exclusions:

Provided in section 1.12.14

Pursuant to 21 CFR Sections 25.15 and 25.31(a), Alvogen Pine Brook, Inc. claims a categorical exclusion from the requirement to prepare an Environmental Assessment Statement.

III. List of Deficiencies To Be Communicated

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 204403

APPLICANT: Alvogen Pine Brook, Inc.

DRUG PRODUCT: Rivastigmine Transdermal System; 4.6mg/ 24hr, 9.5mg/ 24hr, and 13.3mg/ 24hr

The following deficiencies listed below may be delivered via the easily correctable deficiency method (10 day firm response expected) if the situation allows YES NO

A. Deficiencies

1. The Drug Master File (DMF) ^{(b)(4)} for Rivastigmine was reviewed and found inadequate. The DMF holder, ^{(b)(4)} was notified of the deficiencies in a letter sent on April 3, 2012. The DMF holder has submitted an amendment in response to this letter and the DMF, as amended, is under review.

2.  ^{(b)(4)}

3.

4.

5.

6.

7.

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39.

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44.

45.

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47.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide any additional stability data that is available for the drug product.
2.  (b) (4)
3. For each product strength, please provide Rivastigmine Transdermal System samples of the RLD and applicant's drug product.
4. Please update the Master Batch Records to include changes resulting from this letter.

The establishments referenced in the application should be in compliance with cGMP at the time of approval.

ADMINISTRATIVE**A. Reviewer's Signature****B. Endorsement Block**

Norman E. Ohler/12/10/2013

Chemistry Team Leader Name/Date: 02/26/2014

Project Manager Name/Date: Hany S Edward, 3/7/14

TYPE OF LETTER:

Not Approvable (not easily correctable deficiencies) – Major.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN E OHLER
03/07/2014

HANY S EDWARD
03/07/2014

BHAGWANT D REGE
03/07/2014

BING CAI
03/07/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 204403

PHARM/TOX REVIEWS

Office of Generic Drugs, Division of Clinical Review

Pharmacology/Toxicology Consultation

Rivastigmine Film, Transdermal Patch, 4.6 mg/24 h (5 cm²), 9.5 mg/24 h (10 cm²), and
13.3 mg/24 h (15 cm²)

Drug Product:	Rivastigmine Transdermal System
ANDA:	204403
ANDA Sponsor:	Alvogen Pine Brook, Inc.
Reference Listed Drug:	Exelon® Patch (Rivastigmine Transdermal System); NDA 22083
RLD Sponsor:	Novartis Pharmaceutical Corporation
Pharmacology-Toxicology Primary Reviewer:	Melanie Mueller, PhD Staff Fellow (Toxicologist) Division of Clinical Review, Office of Generic Drugs
Pharmacology-Toxicology Secondary Reviewer:	Robert Dorsam, PhD Pharmacology/Toxicology Team Leader Division of Clinical Review, Office of Generic Drugs
Tertiary Reviewer	Daiva Shetty, MD Acting Deputy Division Director Division of Clinical Review, Office of Generic Drugs
To:	Suneela Prodduturi, CMC Reviewer, Division of Modified Release Products (DMRP)/Office of Live Cycle Drug Products (OLDP)/ Office of Pharmaceutical Quality (OPQ)
Reason for Consult:	The Drug Product Quality Review Team of OPQ requested a Pharm/Tox Consult regarding acceptability of the firm's proposed limit of (b) (4) of the impurity (b) (4) (b) (4)
Material Reviewed:	Toxicology Assessment of (b) (4) Toxicology Data of (b) (4) from Published Literature ANDA 204403 CMC Reviews, CR Amendment, IR Response ICH Q3C Guideline for Impurities: Residual Solvents
Date of ANDA Submission:	June 12, 2012
Date of Consult:	May 15, 2015
Date of Completion:	June 13, 2015
Conclusion:	DCR concludes that (b) (4) at a limit of NMT (b) (4) ppm is unlikely to change the safety profile of rivastigmine patch. Hence, the firm's proposal to control (b) (4) at NMT (b) (4) ppm in the specification of the drug product is acceptable from a Pharm/Tox perspective.

1 Executive Summary:

This review addresses a consult request from the Drug Product Quality Review team in the Office of Pharmaceutical Quality (OPQ) regarding acceptable levels of (b) (4), a process by-product of the (b) (4) in a generic Exelon® (rivastigmine) Patch. Alvogen Pine Brook, Inc. is proposing to control (b) (4) with the limit of Not-More-Than (NMT) (b) (4) ppm in their final drug product and the Drug Product Quality Review team is seeking advice whether this limit is acceptable.

The abbreviated new drug application (ANDA) 204403 by Alvogen Pine Brook Inc., who is proposing a generic Exelon® (rivastigmine) Patch, was reviewed. Rivastigmine is indicated for treatment of dementia of the Alzheimer type and that is associated with Parkinson's disease. Upon review of nonclinical toxicology data of (b) (4), the permissible daily exposure (PDE) is two-fold higher than the proposed maximum daily exposure to (b) (4) at its specification limit of NMT (b) (4) ppm, i.e. (b) (4), respectively. Target organs of toxicity included the liver (195-fold safety margin compared to proposed clinical exposure) and the central nervous system. Occupational safety limits provide a 40-fold safety margin compared to the clinical exposure in the proposed generic and neurotoxicity in occupational workers occurred at levels 7,646 times higher than the currently proposed in rivastigmine patch. Furthermore, (b) (4) shows no indication for genotoxicity and dermal studies with (b) (4) in rabbits containing comparable levels of (b) (4) to those proposed in the generic product showed no signs of skin irritation or sensitization. Additionally, other CDER-approved transdermal drug products result in more than two-fold higher exposure levels than the currently proposed (b) (4) levels for the generic rivastigmine patch. Taken together, along with the fact that highest (b) (4) levels measured in exhibit batches of the generic drug product were less than half of the proposed maximum level, (b) (4), respectively, (b) (4) in the rivastigmine patch is not expected to pose an increased safety risk. DCR concludes that (b) (4) at a limit of NMT (b) (4) ppm is unlikely to change the safety profile of rivastigmine patch. Hence, the firm's proposal to control (b) (4) at NMT (b) (4) ppm in the specification of the drug product is acceptable from a Pharm/Tox perspective.

2 Recommendation:

DCR concludes that (b) (4) at a limit of NMT (b) (4) ppm is unlikely to change the safety profile of rivastigmine patch. Hence, the firm's proposal to control (b) (4) at NMT (b) (4) ppm in the drug product is acceptable from a Pharm/Tox perspective.

3 Regulatory Background:

Alvogen Pine Brook, Inc. submitted an Abbreviated New Drug Application (ANDA) 204403 on June 12, 2012, proposing a generic drug product rivastigmine transdermal system. The reference listed drug (RLD) product Exelon® (rivastigmine) Patch is available in the following strengths: 4.6 mg/24 hours, 9.5 mg/24 hours, and 13.3 mg/24 hours. On July 25, 2014, the Agency issued a Complete Response (CR) letter, among other deficiencies asking the firm to submit safety information for the (b) (4) so that a toxicological evaluation could be performed (see deficiency #29) as well as to consult with the excipient DMF holder whether

¹ <http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af80346299>

(b) (4) was used in previously approved drug products (see deficiency #30)¹. On October 10, 2014, Alvogen provided in their response to the CR letter a toxicological assessment of (b) (4) as well as of (b) (4) in (b) (4). The toxicology assessment was based on the classification of a transdermal product to be administered on intact skin². Additionally, the sponsor submitted a comparison of specification limits between (b) (4) and similar (b) (4) (b) (4) listed in the Agency's Inactive Ingredient Database (IID)². As part of a chemistry information request (IR) #106841 issued on April 30, 2015, the sponsor was asked to include drug-product release specification for (b) (4) and to justify their proposed limits³. The firm responded on May 15, 2015 with updated product release specifications that included a test and specification limit for (b) (4) of NMT (b) (4) ppm (see Module 3.2.P.5.1, Table 3)⁴. The sponsor states that the proposed limit is based on the results of the exhibit batches as well as the specification for the raw material (b) (4). Furthermore, the firm justified acceptability of the proposed limit based on the toxicology data submitted to deficiencies #29 and #30 submitted in the October 10, 2014 submission. Subsequently, DCR was consulted on May 25, 2015 to comment on acceptability of the firm's proposed limit of NMT (b) (4) ppm for (b) (4) in rivastigmine transdermal system.

3.1 Orange Book Information

There are three marketed prescription entries in the Orange Book containing the active ingredient rivastigmine (see Table 1 below).

Table 1: Orange Book Currently Approved Applications for Rivastigmine

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N022083		No	Rivastigmine	Film, Extended Release; Transdermal	13.3MG/24HR	Exelon	Novartis
N022083		No	Rivastigmine	Film, Extended Release; Transdermal	4.6MG/24HR	Exelon	Novartis
N022083		Yes	Rivastigmine	Film, Extended Release; Transdermal	9.5MG/24HR	Exelon	Novartis

Source: Search on 06/01/2015 by this reviewer of the Orange Book.

TE=Therapeutic Equivalence

RLD=Reference Listed Drug

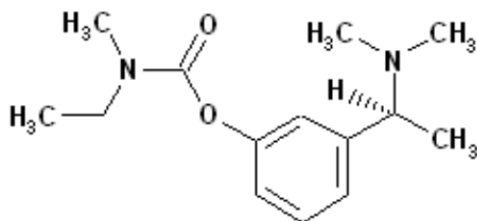
3.2 Description of the RLD Drug Product

Exelon® (rivastigmine) Patch is indicated for the treatment of dementia of the Alzheimer's type (AD) and for the treatment of mild to moderate dementia associated with Parkinson's disease (PDD). Chemically, rivastigmine is (S)-3-[1-(dimethylamino) ethyl]phenyl ethylmethylcarbamate. The molecular formula for rivastigmine is C₁₄H₂₂N₂O₂ as the base and a molecular weight of 250.34 (as the base) with the following structure:

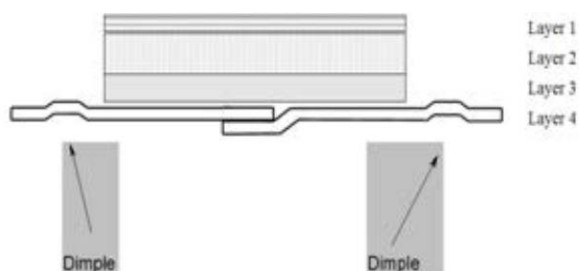
² <\\cdsesub1\evsprod\anda204403\0019\m1\us\12-cover-letters\cover-letter-seq-0019-10-10-14.pdf>

³ <\\cdsesub1\evsprod\anda204403\0025\m1\us\12-cover-letters\information-request-chemistry-reference.pdf>

⁴ <\\cdsesub1\evsprod\anda204403\0025\m1\us\12-cover-letters\cover-letter-seq-0025-5-14-2015.pdf>



Rivastigmine is a viscous, clear, and colorless to yellow to very slightly brown liquid that is sparingly soluble in water and very soluble in ethanol, acetonitrile, n-octanol and ethyl acetate. The distribution coefficient at 37°C in n-octanol/phosphate buffer solution pH 7 is 4.27. Exelon® Patch is for transdermal administration. The patch is a 4-layer laminate containing the backing layer (Layer 1), drug product acrylic matrix (Layer 2), adhesive silicon matrix (Layer 3), and overlapping release liner (Layer 4). The release liner is removed and discarded prior to use.



3.3 Indications

Exelon® Patch is indicated for the treatment of dementia of the Alzheimer's type (AD). Efficacy has been demonstrated in patients with mild, moderate, ^{(b) (4)} Alzheimer's disease. The patch is further indicated for the treatment of mild to moderate dementia associated with Parkinson's disease (PDD). For more details see the RLD product's label⁵ approved on February 3, 2015.

3.4 Dosage and Administration

The following was excerpted from the RLD's drug label:
 Apply a patch on intact skin for a 24-hour period; replace with a new patch every 24 hours. Initiate treatment with 4.6 mg/24 hours Exelon® Patch. After a minimum of 4 weeks, if tolerated, increase dose to 9.6 mg/24 hours, which is the minimum effective dose. Following a minimum additional 4 weeks, may increase dosage to maximum dosage of 13.3 mg/24 hours. More detailed information on dosage and administration of Exelon® Patch can be found in the most recent approved RLD product's label.

3.5 Pregnancy Category

Pregnancy Category B. There are no adequate and well-controlled studies in pregnant women. No dermal reproduction studies in animals have been conducted. Oral reproduction studies in pregnant rats and rabbits revealed no evidence of teratogenicity. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

⁵ http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022083s020lbl.pdf

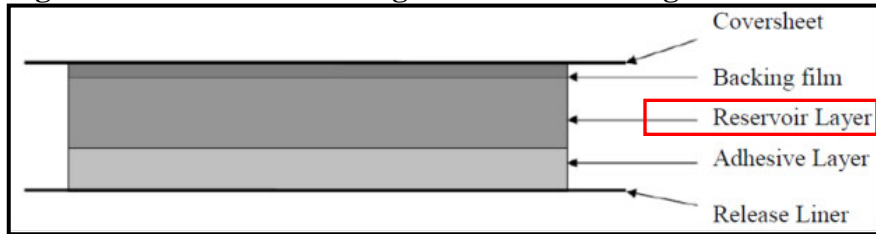
3.6 Mechanism of Action

Although the precise mechanism of action of rivastigmine is unknown, it is thought to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. The effect of rivastigmine may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that rivastigmine alters the course of the underlying dementing process.

4 Discussion:

On May 25, 2015 the chemistry review team of the Office of Pharmaceutical Quality (OPQ) consulted the Division of Clinical Review (DCR) to comment on acceptability of the firm's proposed limit of NMT (b) (4) ppm for (b) (4) in the final drug product rivastigmine transdermal system. Briefly, the generic rivastigmine transdermal system is a matrix patch consisting of two matrix layers (see Figure 1, below).

Figure 1: Schematic Drawing of Generic Rivastigmine Patch



The (b) (4) that contains the active ingredient consists of an (b) (4) forming agent and dispersed rivastigmine free base as the active ingredient (see Table 2, below). The matrix forming adhesive used in the reservoir layer is (b) (4)

(b) (4)⁶

⁶ <http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af8031eee2>

Table 2: Qualitative Composition of Generic Rivastigmine Patch's Adhesive Layers

(b) (4)

(b) (4)

product specification with a limit of NMT 500 ppm . The specification of NMT 500 ppm in the raw material was found to be adequate as (b) (4) levels could further reduce during drying in the final drug product. Hence, it is the ANDA firm's responsibility to ensure adequate control of (b) (4) in their final drug product⁷. Based on residual (b) (4) amounts in nine exhibit batches of the generic rivastigmine patch (see Table 4, below), the applicant proposes a limit of NMT (b) (4) ppm for (b) (4) in their final drug product (see Table 3, below).

Table 3: Drug Product Release Specification for (b) (4)

Adhesive By-Product	Proposed Specification	$\mu\text{g/patch}$ (Finished Product Strength)
(b) (4)	NMT (b) (4) ppm	(b) (4) (4.6 mg/24 hr)
		(9.5 mg/24 hr)
		(13.3 mg/24 hr)

⁷ <http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af80390546>

Table 4: Summary of Residual (b) (4) in Exhibit Batches of Rivastigmine Patch

Residual (b) (4) (ppm)			
Batch Code	Dosage strength	(b) (4) / ppm ¹⁾	(b) (4) / µg/patch
C0002AL0AT	4.6 mg/ 24 hr	203	8.4
C0004AL0AU	9.5 mg/ 24 hr	192	8.0
C0006AL0AT	4.6 mg/ 24 hr	194	8.0
C0008AL0AU	9.5 mg/ 24 hr	196	16.2
C0010AL0AT	4.6 mg/ 24 hr	213	17.6
C0012AL0AU	9.5 mg/ 24 hr	204	16.9
C0014AL0BC	13.3 mg/ 24 hr	191	23.7
C0016AL0BC	13.3 mg/ 24 hr	205	25.5
C0018AL0BC	13.3 mg/ 24 hr	156	19.4

¹⁾ LOQ: 28 ppm per patch

On October 10, 2014 the ANDA applicant submitted a toxicological assessment for (b) (4) towards its use in transdermal drug products applied to intact skin. Additionally, the firm provided a justification for the proposed limit of NMT (b) (4) ppm for (b) (4) that was based on pharmacology/toxicology data. Toxicology data for (b) (4) and the acceptability of the proposed limit are discussed in detail in the sections below.

4.1 Risk Assessment

Toxicology

Per the RLD's label, one rivastigmine patch should be applied for a 24-hour period and be replaced with a new patch every 24 hours. The maximum daily dose (MDD) is 13.3 mg/24 hours⁵. Based on the total weight per patch, the drug product's MDD, and the specification of NMT (b) (4) ppm, the maximum daily exposure to (b) (4) is (b) (4) assuming a body weight of 60 kg (Table 5, below). Previous pharm/tox consults have calculated a Permitted Daily Exposure (PDE) as described in ICH Q3C guidance for residual solvents to determine acceptability of (b) (4) in transdermal drug products and are described further below (see PDE Section and (b) (4) in Previously Approved Products Section, further below).

Table 5: Patch Composition and (b) (4) Amounts per Dosage Strength		4.6	9.5	13.3
Patch Dosage Strength (mg/24 h)				
Total Patch Weight (mg)*		(b) (4)		
Amount (b) (4) / Patch (mg)*		(b) (4)		
Amount (b) (4) / Patch (µg) [#]		(b) (4)		

* Taken from Module 3.3.2.P
[#] Calculated based on specification of NMT (b) (4) ppm and total patch weight

(b) (4)

with the molecular formula (b) (4) and the following structure:



compounds and can be absorbed by the human body either through inhalation or ingestion upon which it might cause convulsion, dizziness, headache, nausea, unconsciousness, and vomiting⁸.

Acute Toxicology

LD 50 values for (b) (4) range from 18-50 mg/kg in several species after administration via various routes and have been reported as detailed in Table 6 below⁹.

Species	Route	LD50 (mg/kg)
Rat	Subcutaneous	30
	Oral	38.9
	Intraperitoneal	17.5
Mouse	Intraperitoneal	17.7
	Intravenous	18
Guinea Pig	Subcutaneous	23
	Oral	17.5
Rabbit	Intravenous	20

In addition, in an acute skin absorption study in which the intact dorsal skin of male albino rabbits was exposed for 24 h to various doses of (b) (4), a dose of 100 mg/kg caused severe adverse effects on the central nervous system, such as restlessness, labored breathing, pupillary constriction, and spasms, ultimately leading to death within 1.5 h of exposure. Lower doses tested (1 and 10 mg/kg) caused acute nervousness, breathing problems, reduced hind leg coordination, and pupillary constriction. In the subsequent days, weight loss, lethargy, and mild skin erythema were noted¹⁰.

Transdermal Absorption

No dermal penetration studies on (b) (4) are available. However, based on the results of the acute dermal toxicity study in rabbits discussed above and the physical properties of (b) (4), absorption of (b) (4) through the skin appears likely. Briefly, (b) (4) low molecular weight of (b) (4) indicate that this chemical might penetrate the intact skin. Furthermore, dermal exposure to the lowest dose of 1 mg/kg caused some neurotoxic signs (see Acute Toxicology Section, above), which supports the notion that (b) (4) enters systemic circulation after dermal absorption.

Genotoxicity

⁸ <http://www.cdc.gov/niosh/ipcsneng/neng1121.html>

⁹ <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+7193>

¹⁰ [http://yosemite.epa.gov/oppts/epatscat8_nsf/by+Service/1D34DCDFBB9F8C5885256930004CDACC/\\$File/8892010553.pdf](http://yosemite.epa.gov/oppts/epatscat8_nsf/by+Service/1D34DCDFBB9F8C5885256930004CDACC/$File/8892010553.pdf)

(b) (4) tested negative for mutagenicity in a standard Ames assay using the pre-incubation method. Briefly, four *S. typhimurium* strains (TA100, TA1535, TA97, and TA98) were exposed to concentrations ranging from 0-10,000 µg of (b) (4) per plate. No dose-dependent increase in revertant number was observed regardless of presence or absence of metabolic activation¹¹. Accordingly, a mouse lymphoma mutagenesis assay that examined the induction of trifluorothymidine-resistant mutant colonies both with and without metabolic activation did not show increased numbers of mutant colonies in L5178Y TK±3.7.C mouse lymphoma cells after exposure to 1,500 to 2,000 µg/mL of (b) (4).

Repeated-Dose Toxicology

During a 90-day repeated dose study, rats (N=15/group/sex) were orally administered (b) (4) at doses of 0.001, 0.01, 0.1, 0.3, 1, 3, and 10 mg/kg/day. (b) (4) resulted in decreased weight gain in males and females at the two highest doses. No treatment related effects were observed in survival, demeanor, food consumption, hematology, or urinalysis. Male rats showed enlarged kidneys with pale, greenish color at 3 mg/kg/day and 10 mg/kg/day. Male, but not female rats showed treatment-related, dose-dependent morphologic kidney changes of degenerative nature at all doses including and higher than 0.1 mg/kg/day. Hyaline droplet formation in tubular epithelial cells was observed that was reversible after a 7 day recovery period. Treatment-related liver changes (enlarged hepatocytes) were observed in males and females at the two highest dose administered. Based on these results, a No-Observed-Adverse-Effect Level (NOAEL) of 0.01 mg/kg/day with regard to kidney toxicity was determined in rats¹³.

During a 90-day repeated dose study Beagle dogs (N=4/group/sex) received (b) (4) via gelatin capsules at doses of 0.3, 1, or 3 mg/kg/day. No treatment-related effects in survival or abnormal behavior were noted at doses up to 3 mg/kg/day. Female dogs showed a slight decrease in weight gain at 3 mg/kg/day. Blood chemistry, as well as corresponding hematological and urine analyses revealed no compound-related effects at any dose level tested, except for elevated blood thiocyanate levels in the 3 mg/kg/day dose group. Liver-to-body weight ratios were statistically elevated at the highest dose, however, it was concluded that this increase was due to overall reduced body weight of the animals and taken together with the absence of correlative abnormal clinical chemistry or histopathological findings supports the conclusion that the liver is not a target organ. No microscopic findings related to (b) (4) ingestion were found at any dose level, including in liver and kidney¹³.

The repeated-dose study in both species was judged by the Health Council of the Netherlands¹⁴ in context of a health hazard assessment of (b) (4) for the purpose of updating occupational exposure limits. The committee considered the liver as the target organ in both species based on the assumption that kidney effects, including hyaline droplet formation, of (b) (4) in male rats are thought to be induced by the accumulation of the male rat-specific protein α -2 μ -globulin, and are hence not considered relevant to man. Subsequently, with regard to macroscopic (rat and dog) and microscopic (rat) liver changes, a NOAEL of (b) (4) was determined

¹¹ <http://tools.niehs.nih.gov/cebs3/ntpViews/?activeTab=detail&studyNumber=002-02892-0001-0000-4>

¹² <http://pubs.acs.org/doi/pdf/10.1021/tx0503552>

¹³ http://ac.els-cdn.com/0272059086901958/1-s2.0-0272059086901958-main.pdf?_tid=b3bd28e4-0969-11e5-b31a-00000aacb35e&acdnat=1433278709_49429921c2161cc2d3edf377b4f1a75e

¹⁴ <http://healthcouncil.eu/sites/default/files/00%4015041OSH.PDF>

in rats and dogs¹⁴. Based on this NOAEL, a 195-fold safety margin between the proposed daily exposure, i.e. 30.7 $\mu\text{g}/\text{m}^2$ (60 kg adult body weight and k_m of 37) and the NOAEL (6000 $\mu\text{g}/\text{m}^2$ with k_m of 6) in rat as most sensitive species was calculated with a consideration that all (b) (4) (i.e. 100%) is systemically absorbed.

Reproductive Toxicology

Pregnant golden Syrian hamsters (N=3-20/dose) received a single intraperitoneal injection of (b) (4) at doses of 4.9, 9.9, or 20 mg/kg at day 8 of gestation (identified critical period of organogenesis in this animal model). Examination of offspring on day 11 of gestation showed suppressed fetal growth (i.e., decreased fetal crown-rump length) at doses of 9.9 mg/kg and higher as well as increased malformation (i.e., exencephaly) at the highest dose. The incidence of malformation, however, did not significantly differ from that in the control group and (b) (4) was found not to be teratogenic. Maternal toxicity was observed at 20 mg/kg expressed as clonic-tonic convulsion and death¹⁵.

Dermal Irritation

No studies were available that evaluate the dermal irritation potential of pure (b) (4). However, as part of the toxicological assessment of (b) (4) the applicant submitted skin irritation studies in which (b) (4) was applied as a 4 cm^2 patch to one intact and one abraded site of the clipped backs of six healthy New Zealand Albino rabbits. The sites were occluded for 24 hours and examined for erythema and edema immediately before and after patch removal, and then 24 hours, 48 hours and 7 days after patch removal. Under the study conditions, (b) (4) did not cause any skin reaction at any observation period and is therefore considered not to be a dermal irritant².

According to the manufacturer specifications, (b) (4) might be contained in (b) (4) at levels up to 500 ppm. Assuming that (b) (4) remains completely in place during the heating process employed to dry coat the patches used in the study, a dry coating weight of the copolymer of 100 mg/m^2 per patch, and the fact that (b) (4) is supplied at approximately 40% solids, the maximum amount of (b) (4) rabbits were exposed to in the skin irritation study was 50 μg . This amount (i.e. 50 μg) is approximately the same as the maximum daily exposure of (b) (4) in the proposed generic product. The details for the calculation are below:

(b) (4)

Dermal Sensitization

No dermal sensitization studies with pure (b) (4) are available. However, as part of the toxicological assessment of (b) (4), the applicant submitted skin sensitization studies in which (b) (4) was applied topically as a 4 cm^2 patch to skin of Hartley Albino guinea pigs once per week for three weeks total². Patch sites were occluded for 6 hours and examined for dermal effects 24 and 48 hours after patch removal. Two weeks after the third

¹⁵ http://ac.els-cdn.com/S0272059083801717/1-s2.0-S0272059083801717-main.pdf?_tid=58215dea-0a0c-11e5-89f6-00000aab0f01&acdnat=1433348563_d359cbbe0053b23416cf568939f1f4b6

induction dose a challenge dose (4 cm² patch) was administered. Skin reactions were examined 24 and 48 hours after patch removal. No skin effects were observed after induction or challenge dose and thus it can be concluded that (b) (4) is not a skin sensitizer under the study conditions.

Applying the calculation from the dermal irritation study, animals were exposed to a maximum of 50 µg of (b) (4) per patch during skin sensitization studies. Doses of (b) (4) of up to 50 µg can be assumed to not cause skin sensitization.

Permitted Daily Exposure

Previous Pharm/Tox consults established safe limits of exposure to (b) (4) in various transdermal drug products using a PDE approach. Briefly, (b) (4) volatile nature renders it suitable to be regarded as residual solvent per ICH Q3C guidance per which residual solvents are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products¹⁶. As such, methods described in ICH Q3C (see equation below) used to establish PDE values can be adapted to determine the pharmaceutically acceptable intake of (b) (4)

$$PDE = NOAEL \cdot \text{Body Weight} / F1 \cdot F2 \cdot F3 \cdot F4 \cdot F5$$

Using data derived from the most relevant study in the most sensitive animal species, i.e. repeated oral dosing in rats, a PDE of 100 µg for (b) (4) was calculated for adults weighing 50 kg using a NOAEL of (b) (4) (see Table 7, below). Per ICH Q3C, this relatively low body weight provides an additional safety factor against the standard weights of 60 kg or 70 kg that are often used in this type of calculations.

Table 7: (b) (4) PDE Based on NOAEL of (b) (4) Obtained in Rats		
		PDE
Adult Body Weight	50 kg	100 µg
F1	Extrapolation from Rat to Human	5
F2	Variability Between Individuals	10
F3	Toxicity Studies of Short Term (3 Month in Rats)	5
F4	Severe Toxicity (Liver)	2
F5	NOEL not Established	1

In conjunction with the total weight of the patch per dosage strength the following concentration limits for (b) (4) in rivastigmine patch were established:

Table 8: (b) (4) Concentration Limits	
Concentration (ppm) = 1000 · PDE (mg/day)/Patch Weight (g/day)	
Patch Weight (mg)	Concentration Limit
(b) (4)	

¹⁶ <http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af802c4e05>

A maximum acceptable concentration limit of 805 ppm for (b) (4) is acceptable in this patient population. The amount of (b) (4) maximally present in the generic rivastigmine patches at the proposed specification of NMT (b) (4) ppm is two-fold lower than the concentration limit per PDE based on (b) (4) amounts found to be safe in animals.

Further Considerations to the Risk Assessment

Occupational (b) (4) Standards

(b) (4) is a by-product during production of (b) (4) and is released into the air and subsequently absorbed by occupational workers. Because of its neurotoxic potential demonstrated in animals in the form of convulsion and death by asphyxia and in occupational workers in form of convulsion, unconsciousness, strong headaches, nausea, vomiting, salivation and disturbance of equilibrium, the National Institute for Occupational Safety and Health (NIOSH), the American Conference of Industrial Hygienists (ACGIH), and the Occupational Safety and Health Administration (OSHA) set occupational exposure levels for (b) (4) (b) (4) for a conventional 8-h workday and a 40-h work week with skin notation¹⁸. A health-based re-assessment of administrative occupational exposure limits conducted by the Health Council of the Netherlands (comprised of ACHIG, NIOSH, and OSHA) used the NOAEL of (b) (4) from above described sub-chronic rat study to determine a revised occupational exposure level of 0.2 mg/m³ for an 8-h workday or 0.036 ppm¹⁴. Assuming 100% absorption and a breathing volume of 10 m³ per working day, exposure to 2000 µg/day of (b) (4) is thought to be safe in the occupational industry, leading to a 40-fold safety margin when compared to proposed daily levels in rivastigmine patch, i.e. (b) (4). Indeed, a study that monitored (b) (4) levels in the (b) (4) industry after occurrence of (b) (4) intoxication (particularly convulsion, headaches, dizziness, and unpleasant taste) showed that as levels of (b) (4) were decreased to 3 mg/m³ and below (0.1 – 0.9 mg/m³) the symptoms disappeared. Of note, convulsion in four occupational workers were reported at (b) (4) concentrations up to 38 mg/m³, a value 7,646-fold higher than the proposed maximum daily exposure in rivastigmine patch. In conclusion, occurrence of neurotoxic side effects seems unlikely at the proposed (b) (4) level in the generic rivastigmine patch.

(b) (4) in Previously CDER-Approved Drug Products

A DARRTS Communication Content Search was performed to identify other CDER-approved drug products in which a specification of (b) (4) was reviewed and PDE established for other drug products. Particular attention was given to whether approved levels exceed the daily exposure amounts, i.e. (b) (4), at the currently proposed limit of NMT (b) (4) ppm.

ANDA 90873: Clonidine Transdermal System, 0.1, 0.2, and 0.3 mg per day

This controlled-release, transdermal film is indicated for hypertension in adult patients.

Clonidine controlled-release transdermal film potentially contains (b) (4) as a by-product from (b) (4) which is used as skin adhesive and API reservoir in this drug product.

According to a pharm/tox consult recommendation from February 14, 2013, (b) (4) is controlled

¹⁷ <http://web.a.ebscohost.com/ehost/pdfviewer/pdfviewer?vid=2&sid=a6eb988c-5bbb-4bb6-ba06-95f85d328970%40sessionmgr4005&hid=4107>

¹⁸ <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~IqRRFH:1>

at NMT (b) (4) ppm in the transdermal film which leads to maximum daily exposure of 117 µg/day of (b) (4) at the drug product's MDD^{16,19}. Notably, a PDE of 120 µg (b) (4)/day was established in the pharm/tox review based on a NOAEL of (b) (4) based from the same sub-chronic rat described above. For PDE calculation an average body weight of 60 kg was assumed resulting in a slightly higher acceptable level compared to the PDE established in this review (see *Permitted Daily Exposure* section, above).

NDA 21306: Butrans® (buprenorphine) Transdermal System, 5, 7.5, 10, 15, and 20 µg/hour
This controlled-release, transdermal patch is an opioid analgesic indicated for around-the-clock management of moderate to severe chronic pain for an extended period of time. Butrans® controlled-release, transdermal patches potentially contain (b) (4), derived as by-product from (b) (4) (skin adhesive and active pharmaceutical ingredient (API) reservoir) and (b) (4) (skin adhesive). (b) (4) is controlled at (b) (4) ppm in Butrans® transdermal patches which leads to a maximum daily exposure of (b) (4) of (b) (4) in adult patients weighing 50 kg²⁰. In the context of the NDA's chemistry review, a PDE for (b) (4) was not calculated but the sponsor established a safety margin based on the NOAEL of 1 mg/kg/day in rats without applying any additional safety factors.

Comparison to the RLD

The API reservoir in the RLD product Exelon® (rivastigmine) patch contains an (b) (4) that differs from (b) (4). According to the acrylic pressure sensitive adhesive's specifications, it is tested for appearance, identity, viscosity, solids content, sulphated ash, heavy metals, and residual monomers. A specification for residual solvents or impurities such as (b) (4) is not included²¹. Sufficient manufacturing process information for this particular (b) (4) could not be obtained to identify if (b) (4) is a by-product. Considering the volatile nature of (b) (4), it is possible that some of this compound could sublime during the drying process when the adhesive is fixed to the final drug formulation. Indeed, the highest amounts of (b) (4) detected in exhibit batches were only about half the maximum amount possible at the proposed limit of NMT (b) (4) ppm (see Table 4, above in Section 4; Discussion). (b) (4) levels (b) (4) are not expected to change the safety profile of the generic drug product compared to the RLD. Furthermore, based on occupational exposure data and limits, (b) (4) at its proposed maximum daily exposure of (b) (4) is unlikely to induce neurotoxicity (see above), which otherwise would be of concern in the present patient population.

5 Conclusions and Recommendations:

The nonclinical toxicology data for (b) (4) supported the calculation of a PDE that is two-fold higher than the proposed maximum daily exposure to (b) (4) at its specification limit of NMT (b) (4) ppm, (i.e. PDE: (b) (4) respectively). Target organs of toxicity included the liver (195-fold safety margin compared to proposed clinical exposure) and

¹⁹ <http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af802b9974>

²⁰ <http://darrrts.fda.gov:9602/darrrts/ViewDocument?documentId=090140af801dc87b>

²¹ <\\cdsesub1\evsprod\nda022083\0046\m3\32-body-data\32p-drug-prod\exelon-patch-transdermal-system-13-3-mg--24hrs-01\32p4-contr-excip\acrylic-pressure-sensitive-adhesive\specifications-acrylicadhesive.pdf>

the central nervous system. Occupational safety limits provide a 40-fold safety margin compared to the clinical exposure in the proposed generic and neurotoxicity in occupational workers occurred at levels 7,646 times higher than the proposed (b) (4) levels in rivastigmine patch. Furthermore, (b) (4) shows no indication for genotoxicity and dermal studies with (b) (4) (b) (4) in rabbits showed no signs of skin irritation or sensitization at comparable levels of (b) (4) to those proposed in the generic product. Additionally, specification limits for (b) (4) in CDER-approved transdermal drug products result in more than two-fold higher exposure levels than are proposed for the current generic rivastigmine patch. Taken together with the fact that highest (b) (4) levels measured in exhibit batches of the generic drug product were less than half of the proposed maximum level, (b) (4) respectively, (b) (4) in the rivastigmine patch is not expected to pose an increased safety risk. DCR concludes that (b) (4) at a limit of NMT (b) (4) ppm is unlikely to change the safety profile of rivastigmine patch. Hence, the firm's proposal to control (b) (4) at NMT (b) (4) ppm in the specification of the drug product is acceptable from a Pharm/Tox perspective.

6 References:

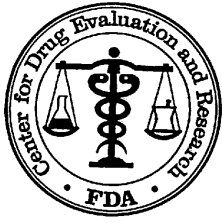
See Footnotes

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 204403

STATISTICAL REVIEWS



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

ANDA/Serial Number: 204403

Drug Name: Rivastigmine Transdermal System (TDS)
4.6 mg/Patch 24 Hours

Indication(s): Treatment of mild to moderate dementia of the Alzheimer's and Parkinson's disease

Reference Listed Drug: Exelon 4.6 mg/24 Hours Patch

Applicant: Alvogen Inc.

Date(s): June 12, 2012

Biometrics Division: DB6

Statistical Reviewer: Guoying Sun, Ph.D.

Concurring Reviewers: Vicki Lancaster, Ph.D.

Medical Division: Clinical team in OGD

Clinical Team: Daiva Shetty, M.D.

Keywords: irritation, sensitization, adhesion, non-inferiority, matched pair analysis

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1 Executive Summary

1.1 Conclusions and Recommendations

The purpose of the studies was to assess the irritation, sensitization, and adhesion properties of the test patch versus the reference patch. The test patch was found to be non-inferior to the reference patch for irritation and sensitization, and the test and reference patches met the adhesion criterion based on the memo, “Waiver of Statistical Non-Inferiority Analysis for Highly Adhering Patch Drug Products, February 10, 2014.”

1.2 Brief Overview of the Clinical Studies

This application consists of two studies: a two-period irritation and sensitization study #C10-1870 and an adhesion study #R10-1307.

1.2.1 Irritation and Sensitization Study (#C10-1870)

The objectives of this study were to confirm that the test product was no more irritating and sensitizing than the reference product when applied over a continuous 21 day Induction Phase followed by a 48 hour Challenge Phase.

This was a multiple-site, randomized, multiple-application, evaluator-blinded, controlled study to compare the cumulative irritation and sensitization potential of Alvogen’s formulation of Rivastigmine Patch (Transdermal System), 4.6 mg/24 hours to the already marketed product Exelon Patch (Rivastigmine Transdermal System), 4.6 mg/24 hours distributed by Novartis Pharmaceuticals Corporation. One-half cut patch of the 4.6 mg/24 hour test formulation and one-half cut patch of the 4.6 mg/24 hour reference formulation was applied to the upper arms during the Induction Phase and to separate sites on the upper back during the Challenge Phase. The location of the patches was randomized either to the left or right upper arm during the Induction Phase and either to the left or the right side of the upper back during the Challenge Phase. No re-challenge phase was conducted in this study.

A total of 280 subjects were enrolled and 262 completed the Induction Phase of the study.

1.2.2 Adhesion Study (#R10-1307)

The objective of this study was to assess the adhesion of Rivastigmine 9.5 mg/24 hours Patch (Transdermal System) compared to that of Exelon 9.5 mg/24 hours Patch (Rivastigmine Transdermal System) following a 24-hour application period in healthy adult subjects. Adhesion study was done together with PK study.

This was a randomized, single-dose, 2-period, 2-treatment, open-label crossover adhesion study conducted under fasting conditions. A total of 30 healthy adult subjects (male and female) were enrolled in the study. Patch adhesion was evaluated at 0 (immediately following patch application), 2, 4, 6, 8, 10, 12, 18, and 24 hours ($\pm$ 10 minutes) after patch application.

1.3 FDA Statistical Results and Issues

Irritation and Sensitization Study (#C10-1870)

Irritation

I) Analyses based on mean cumulative irritation scores:

The non-inferiority analyses based on the mean cumulative irritation scores (primary endpoint) showed that the - 95% upper confidence limit (UCL) for the adjusted mean difference ($\mu_T - 1.25\mu_R$) was less than zero (-0.3728). The non-inferiority test passed therefore the irritation potential of the test patch is considered no worse than that of the reference patch.

II) Analyses based on dichotomized mean cumulative irritation scores:

In addition to the primary endpoint analyses, analyses of the secondary endpoints were conducted to compare the test and reference with regard to the proportions of subjects who had mean cumulative irritation scores greater than or equal to 1 and to 2. Based on the 95% UCL for the difference in proportions, the test can exceed the reference by at most 2.4 percentage points with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 1 ($p_T - p_R = -1.5\%$). In addition, the test can exceed the reference by at most 3.0 percentage points with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 2 ($p_T - p_R = 1.2\%$).

III) Analyses based on dichotomized irritation scores:

The test and reference patches were compared with regard to the proportion of patch applications with irritation scores of 1 or greater for each study day. The 95% UCLs for study Days 8, 15, and 22 were 0.035, 0.021, and 0.017 respectively. That is, the test product can exceed the reference product by at most 3.5, 2.1, and 1.7 percentage points for Days 8, 15, and 22 respectively. In addition, the test and reference patches were compared with regard to the proportion of patch applications with scores of 2 or greater. The 95% UCLs for Days 8, 15, and 22 were 0.045, 0.022, and 0.025 respectively. That is, the test product may exceed the reference product by at most 4.5, 2.2, and 2.5 percentage points for Days 8, 15, and 22 respectively.

Sensitization

Forty-three subjects (43/228 or 18.9%) in the PPPS demonstrated a possible sensitization reaction to both transdermal systems in the Challenge Phase. Of the 43 subjects, no subject demonstrated a possible sensitization reaction for only the test product or only the reference product. As the propensity for causing sensitization for test product A and reference product B was the same, a re-challenge was not conducted to confirm sensitization.

The test patch can exceed the reference patch by at most 1.3 percentage points based on the 95% UCL for the difference in sensitization rates.

Adhesion Study (#R10-1307)

The adhesion data showed that on average 90% of the test patches and 92% of the reference patches had $\geq 90\%$ adhesion for the study duration. The products met or exceeded the adhesion criterion of 90/90 ($\geq 90\%$ of patches having $\geq 90\%$ adhesion throughout the entire study). Therefore, the study passed the adhesion waiver requirement. However, the sample size (27 subjects) did not meet the recommendation of a minimum of 60 subjects.

2 Introduction

2.1 Overview

Rivastigmine is a reversible cholinesterase inhibitor, indicated for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's disease. It was originally approved by FDA as immediate-release capsule (NDA 020823) and oral solution (NDA 021025) formulations on March 21, 2000. A transdermal formulation of rivastigmine was approved on July 6, 2007 (NDA 022083).

This review focuses on the studies submitted to ensure that the skin irritation and sensitization potential of this proposed generic topical patch product are no greater than those of the reference and that the generic product adheres to the skin as well as the reference over the intended duration of wear.

2.2 Data Sources

The data were submitted electronically. The data files are located in the following directories:

Irritation and Sensitization study (#C10-1870)

<\\cdsesub1\evsprod\anda204403\0000\m5\datasets\is-study\datasets\c10-1870\listings>

Adhesion study (#R10-1307)

<\\cdsesub1\evsprod\anda204403\0000\m5\datasets\adhesive-study\datasets\r10-1307\listings>

3 Statistical Evaluation

3.1 Statistical Methodologies

Each subject received a test and reference patch simultaneously in both studies, the skin irritation and sensitization study (#C10-1870) and in the adhesion study (#R10-1307). As a result, observations taken from the same subject are correlated. For the analysis of continuous data, linear mixed models were used; the random effect in the mixed model assessed the correlation within subjects. For matched pair dichotomous data, the McNemar and Clopper-Pearson tests were used to compare the difference between the test and the reference proportions.

3.1.1 Continuous data

<Mixed Model>

The statistical reviewer used a mixed model with treatment (TRT) as a fixed effect and SUBJECT as a random effect to analyze the mean cumulative irritation score and adhesion score.

The statistical method for continuous data uses the estimate of the adjusted mean difference, $\mu_T - 1.25\mu_R$, to test the hypotheses

$$H_0: \mu_T - 1.25\mu_R > 0 \quad \text{vs} \quad H_1: \mu_T - 1.25\mu_R \leq 0$$

where μ_T is the mean response for the test and μ_R is the mean response for the reference. 95% UCLs were obtained based on the estimated means. If the UCL is less than or equal to 0, the null hypothesis is rejected and the test is considered non-inferior to the reference, otherwise it is concluded that the test is worse than the reference.

The SAS® (Version 9.3) PROC MIXED statements for the relevant analysis are

```
Proc Mixed Data = <dataset name>;  
Class Subject TRT;  
Model X = TRT/DDFM = SATTERTH;  
Repeated TRT / sub = Subject type = fa0(2) r;  
Estimate 'Test - 1.25*Reference' int -0.25 TRT 1 -1.25/cl alpha = 0.1;  
LSMEANS TRT;  
Run;
```

3.1.2 Binary data

<Matched pairs dichotomized analysis>

Additional (secondary) endpoints considered were the dichotomized mean cumulative irritation score, irritation score per evaluation time, rate of sensitization, dichotomized mean cumulative adhesion score, and adhesion score per evaluation time. Methods based on the work of McNemar, Clopper-Pearson, and Schuirmann were used to compare the test and reference with regard to binary endpoints (proportions). The McNemar test is a common method for matched pair dichotomized analysis. The Clopper-Pearson method is an “exact” test for small proportions. Schuirmann (2008) examined another method and showed it better preserves type I error for small proportions. The testing procedure was as follows.

For each method used to assess the non-inferiority of the test versus reference, a 95% UCL for the difference of the proportions between test and reference was calculated.

Let

p_T = rate of the test, p_R = rate of the reference (p_T and p_R might be irritation rates, sensitization rates, or adhesion rates depending on the analysis);
 n = total number of subjects;
 b = number of subjects with a negative outcome (irritation, sensitization, or detachment) using the test but not the reference;
and c = number of subjects with a negative outcome (irritation, sensitization, or detachment) using the reference but not the test.
Hypotheses: $H_0: p_T - p_R > \delta$ vs $H_1: p_T - p_R \leq \delta$

Data on two outcomes from matched pairs

		Reference	
		Score $\geq$ crit*	Score $<$ crit
Test	Score $\geq$ crit	a	b
	Score $<$ crit	c	d
Total $n = a + b + c + d$			

*Critical value (crit) used to dichotomize the score.

The difference of $p_T - p_R$ is estimated by the quantity $(b - c)/n$.

Based on McNemar's test, the 95% upper confidence limit (UCL_M) for the quantity $p_T - p_R$ was calculated as

$$UCL_M = \frac{(b - c)}{n} + \frac{1}{n} + 1.645 \sqrt{\frac{(b + c) - \frac{(b - c)^2}{n}}{n}}$$

Based on the Clopper-Pearson test (1934), the 95% upper confidence limit (UCL_{CP}) for the quantity $p_T - p_R$ was calculated as:

$$UCL_{cp} = \left[1 + \frac{n - x}{(x + 1) F_{2(x+1), 2(n-x), \alpha/2}} \right]^{-1} \quad \text{if } b \geq c$$

or,

$$UCL_{cp} = \left[1 + \frac{n - x + 1}{x F_{2x, 2(n-x+1), 1-\alpha/2}} \right]^{-1} \quad \text{if } b < c$$

where $x = |b - c|$ and $\alpha = 0.10$. $F_{2(x+1), 2(n-x), \alpha/2}$ denotes the $(1 - \alpha/2)$ quantile from the F distribution with degrees of freedom $2(x + 1)$ and $2(n - x)$ and $F_{2x, 2(n-x+1), 1-\alpha/2}$ denotes the $\alpha/2$ quantile from the F distribution with degree of freedom $2x$ and $2(n - x + 1)$.

For any given non-inferiority bound δ , the null hypothesis H_0 may be rejected if the 95% UCL for the quantity $p_T - p_R$ is less than or equal to δ , that is UCL_M or $UCL_{CP} \leq \delta$. Rejection of the null hypothesis, H_0 , supports the conclusion of non-inferiority of the test to the reference. Note, the non-inferiority standard, δ , has yet to be decided by OGD.

3.2 Evaluation of Irritation and Sensitization

3.2.1 Study Design and Endpoints

Objectives

The objectives of this study are to confirm that the test product is no more irritating and sensitizing than the reference product when applied over a continuous 21 day Induction Phase followed by a 48 hour Challenge Phase.

Study Design

This was a multiple-site, randomized, multiple-application, evaluator-blinded, controlled study to compare the cumulative irritation and sensitization potential of Alvogen’s formulation of Rivastigmine Patch (Transdermal System), 4.6 mg/24 hours to that of the already marketed product Exelon Patch (Rivastigmine Transdermal System), 4.6 mg/24 hours distributed by Novartis Pharmaceuticals Corporation.

The study consisted of two phases, a 21-day Induction Phase followed by a 14 to 17 day rest period, and a Challenge Phase. During the Induction Phase (Days 1-22), subjects received one-half patch of the test product and one-half patch of the reference product applied simultaneously to different upper arms. The test product and reference product were applied to the same sites every day on Days 1-21, for a total of 21 applications. The location of the patches was randomized either to the right or left upper arm. Approximately 30 minutes (± 10 minutes) after patch removal on Days 2-22 the irritation was evaluated using the irritation rating scale.

Following a 14-day rest period, the Challenge Phase began on Day 36 where subjects received one-half patch of the test product and one-half patch of the reference product applied to skin sites on the upper back for 48 hours ± 4 hours. After patch removal on Day 38, assessments of the sites of application were made at approximately 30 minutes (± 10 minutes) and 24, 48, and 72 hours (± 2 hours) for the appearance of skin reactions indicative of sensitization.

Irritation study: Induction period (Study Days 2 to 22)	Rest period (14 days)	Sensitization study: Challenge period (Study Days 36 to 41)

Treatments

Treatment Code	Description
A (test)	Rivastigmine Transdermal System, 4.6 mg/24 hours*
B (ref.)	Exelon 4.6 mg/24 hours Patch (Rivastigmine Transdermal System)**

*Patch manufactured by (b) (4) (Lot No. C0002AL0AT); **Patch manufactured by LTS Lohmann Therapy Systems Corp.

Outcome Variables

The following scales were used by the sponsor for evaluating both irritation and sensitization.

Scoring Scale for Evaluation of Induction and Challenge Phase Applications:

Dermal responses:

0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; minimal edema or minimal papular response
3	Erythema and papules
4	Definite Edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

Other Effects:

A	(0) Slight glazed appearance
B	(1) Marked glazing
C	(2) Glazing with peeling and cracking
F	(3) Glazing with fissures
G	(3) Film of dried serous exudates covering all or part of the patch site
H	(3) Small petechial erosions and/or scabs

Endpoints

Primary Endpoint

The primary endpoint, mean cumulative irritation score, was the mean of the combined “Dermal Response” and “Other Effect” irritation scores recorded over the Induction period (Study Day 2 to Study Day 22).

Secondary Endpoints:

- Proportion of subjects who had mean cumulative irritation scores ≥ 1
- Proportion of subjects who had mean cumulative irritation scores ≥ 2
- Proportion of subjects who had irritation scores ≥ 2 on Days 8, 15, and 22.

3.2.2 Patient Disposition

Irritation Study

Irritation Study population

A total of 280 healthy adult subjects were enrolled in this study and 262 subjects completed the Induction Phase. Each subject received both study treatments simultaneously during the study.

Demographics

Table 1 shows the distribution of age, gender, and race for the Sponsor's Intent-to-Treat Irritation (ITTI) population and the Per-Protocol Population for Irritation (PPPI).

Table 1: Demographic characteristics for the Sponsor's ITTI and PPPI population

	ITTI N=280	PPPI N=262
Age (years)		
Mean (Range)	39.7 (18-65)	39.8 (18-65)
Gender		
Male	76 (27.1%)	71 (27.1%)
Female	204 (72.9%)	191 (72.9%)
Race		
American Indian or Alaskan Native	3 (1.1 %)	2 (0.8 %)
Asian	2 (0.7 %)	1 (0.4 %)
African American	50 (17.9 %)	46 (17.6%)
White	222 (79.3 %)	210 (80.2 %)
White and American Indian or Alaskan Native	2 (0.7 %)	2 (0.8 %)
White and Asian	1 (0.4 %)	1 (0.4 %)

Sensitization study

Sensitization study population

Table 2 shows the distributions of age, gender, and race for the Sponsor's Sensitization Per-Protocol Population (PPPS). Two hundred thirty healthy adult subjects entered into the study. The per-protocol population for sensitization for the Challenge Phase included 229 of 230 subjects for test product A and 228 of 230 subjects for preference product B.

Table 2: Summary of Demographic Data – the Sponsor’s PPPS Population

	Test N=229	Reference N=228
Age (years)		
Mean (Range)	40.1 (18-65)	40.2 (18-65)
Gender		
Male	64 (27.95%)	63 (27.6%)
Female	165 (72.05%)	165 (72.4%)
Race		
American Indian or Alaskan Native	1 (0.44%)	1 (0.44%)
Asian	1 (0.44%)	1 (0.44%)
African American	39 (17.03%)	39 (17.11%)
White	185 (80.79%)	184 (80.7%)
White and American Indian or Alaskan Native	2 (0.87%)	2 (0.88%)
White and Asian	1 (0.44%)	1 (0.44%)

The primary analysis of sensitization used the PPPS and compared the number and percentage of sensitization reactions (irritation score greater than or equal to 2 at 48 or 72 hours post removal) observed with each patch type.

3.2.3 Results and Conclusions

3.2.3.1 Sponsor’s Analysis Results

Statistical Results of Induction Phase Irritation Analysis (PPPI Population N=262) (Clinical Study Report C10-1870 (R10-1318, S11-0069), page 46, Table 11.4.1.)

Variable	Hypotheses	A-1.25B	Upper Bound of One-Sided 95% Confidence Limit
Cumulative Irritation Scores (Dermal Response + Other Effect Scores) (Test – 1.25*Reference)	$H_0: \mu T - 1.25 \mu R > 0$ $H_1: \mu T - 1.25 \mu R \leq 0$	-8.60592	-7.82006

*A = Test Product, B = Reference Product

The 95% UCL was less than zero therefore one can conclude the test product is non-inferior to the reference product.

3.2.3.2 FDA Results for Irritation and Sensitization study

A) Irritation study

Medical Reviewer’s Comments:

“According to the protocol, subjects were not supposed to take any anti-inflammatory medication except for aspirin or acetaminophen. Two subjects in the study were taking aspirin on a daily basis, one (subject (b) (6)) was on 81 mg, the other one (subject (b) (6)) on 325 mg dose. Only one subject used acetaminophen 500 mg once.

Please exclude the following subjects from the PPPI: (b) (6) (as per the Sponsor’s exclusions) and additional two subjects (b) (6) and (b) (6) ”

Patch moving in the induction period

When a strong irritation reaction occurred, the patch was moved to another site in the Induction Phase of the study. If the patch was moved or completely removed due to a strong irritation reaction, the total irritation score before moving was carried forward for statistical analysis (LOCF).

Primary endpoint: Mean Cumulative Irritation scores

Table 3 shows the descriptive statistics of the cumulative irritation scores for the PPPI by treatment.

Table 3: Summary of Descriptive Statistics for Cumulative Combined Irritation Scores for Test Product and Reference Product Using LOCF

Cumulative Irritation Scores (Dermal Response + Other Effects)	Test Product: Rivastigmine Transdermal System, 4.6 mg/24 hours	Reference Product: Exelon Patch (Rivastigmine Transdermal System) 4.6 mg/24 hours
N	260	260
Mean (Standard Deviation)	32.1(18.6)	32.6(17.7)
Median	33.5	35
Maximum	121	121
Minimum	2	2

Table 4 presents the frequency of the combined dermal response and other effects scores for the test and reference on study Days 8, 12, and 22.

Table 4: Frequency of irritation scores using LOCF (PPPI, N=260)

Visit Day	Treatment	Scores						
		0	1	2	3	4	5	6
Day 8	Test	59	144	72	3	9	1	2
	Reference	43	112	92	2	8	2	1
Day 15	Test	16	84	124	6	21	6	3
	Reference	15	79	134	7	17	6	2
Day 22	Test	6	74	118	18	32	9	3
	Reference	6	75	123	12	34	8	2

Table 5: Analysis for the mean cumulative irritation scores using mixed model (PPPI) (N=260)

Test (Mean μ_T)	Reference (Mean μ_R)	$\mu_T - 1.25\mu_R$	Upper limit one-sided 95% ($\mu_T - 1.25\mu_R$)	Pass the Non-inferiority test
1.5237	1.5502	-0.4104	-0.3728	Yes

Non-inferiority analyses based on the mean cumulative irritation scores (primary endpoint) showed that the 95% UCL for the adjusted mean difference ($\mu_T - 1.25\mu_R$) was less than zero therefore the irritation potential of the test patch is no worse than that of the reference patch.

Secondary endpoints: dichotomized variables

Secondary endpoints examined include the dichotomized mean cumulative irritation scores and irritation scores at visit Days 8, 15, and 22. Analyses of these endpoints are discussed below.

Dichotomized Mean Cumulative Irritation Scores

In addition to the primary endpoint analysis, analyses for the secondary endpoints were conducted to compare the test and reference with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 1 and 2. Sometimes, the proportions for test are lower than the proportions for reference ($p_T - p_R < 0$). Based on the 95% UCL for the difference in proportions, the test can exceed the reference by at most 2.4 percentage points with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 1 ($p_T - p_R = -1.5\%$). In addition, the test can exceed the reference by at most 3.0 percentage points with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 2 ($p_T - p_R = 1.2\%$). Table 6 summarizes the results of the analyses.

Table 6: Analysis of the dichotomized mean cumulative irritation scores

Critical value (crit)	Score $\geq$ crit for Test & not for Reference	Score $\geq$ crit for Reference & not for Test	$p_T - p_R^*$	95% UCL [#] for $p_T - p_R$	
				McNemar	Clopper
1	3	7	-.0154	0.0237	-0.0052
2	10	7	0.0115	0.0299	0.0296

* p_T = mean cumulative irritation score $\geq$ to crit for test and p_R = mean cumulative irritation score $\geq$ crit for reference.

[#]The highest UCL is marked in bold.

Dichotomized Irritation Scores at visit Days 8, 15, and 22

Based on the 95% UCL for the difference in proportions, the test can exceed the reference by at most 1.7 percentage points (on Day 22) with regard to the proportion of subjects who had irritation scores greater than or equal to 1. Also, the test can exceed the reference by at most 2.5

percentage points (at Day 22) with regard to the proportion of subjects who had irritation scores greater than or equal to 2. Table 7 shows the results.

Table 7: Analysis of the dichotomized irritation scores for each study day (PPPI)

Visit Critical value (crit)	Score $\geq$ crit for Test & not for Reference	Score $\geq$ crit for Reference & not for Test	$p_T - p_R^*$	95% UCL [#] for $p_T - p_R$	
				McNemar	Clopper
<i>Crit=1</i>					
Day 8	5	21	-0.0615	0.0353	-0.0375
Day 15	3	4	-0.0038	0.0206	-0.0002
Day 22	2	2	0	0.0165	-0.0115
<i>Crit=2</i>					
Day 8	13	31	-0.0692	0.0449	-0.0433
Day 15	1	7	-0.0231	0.0215	-0.0100
Day 22	6	5	0.0038	0.0248	0.0181

* p_T = mean cumulative irritation score $\geq$ crit for test), and p_R = mean cumulative irritation score $\geq$ crit for reference.

[#]The highest UCL is marked in bold.

B) Sensitization study

From Clinical Reviewer's Comments:

“The proportion of subjects positive to sensitization was similar in both treatment groups. Most of those who developed irritation to the patches in the Challenge phase had a score of 1 or 2. Only three subjects (b) (6) in the test product A arm and four subjects (b) (6) (b) (6) in the reference product B arm developed irritation scores of 4-5. The draft guidance on rivastigmine recommends a re-challenge test four to eight weeks following the original challenge for all subjects with a potential sensitization reaction. The study protocol states that subjects who demonstrate a potentially sensitizing response to either patch may be re-challenged to both test and reference patches at the request of the study Sponsor. The Sponsor chose not to do this based on the fact that none of the subjects developed sensitization to only one of the tested patches. This is acceptable.”

Table 8 presents the frequency of irritation scores for the Challenge period for the Sensitization Per-Protocol population (PPPS).

Table 8: Frequency of irritation scores for the Challenge period (PPPS)

Evaluation Day	Treatment	Combined Irritation score					
		0	1	2	3	4	5
30 min	Test	58	69	100	2	0	0
	Reference	52	72	102	2	0	0
24 hours	Test	82	86	59	0	0	2
	Reference	81	88	58	0	0	1
48 hours	Test	114	75	37	0	0	3
	Reference	111	77	36	0	0	4
72 hours	Test	169	30	24	0	3	3
	Reference	171	27	24	0	3	3

If the scoring for irritation at either the 48 or 72 hour post Day 38 removal was greater than or equal to 2 on the irritation scale, or demonstrated a persistent and intense score judged by the investigator to be suggestive of a sensitization reaction, then the subject was considered to demonstrate a possible sensitization response to that specific patch type.

Table 9: Frequency Distribution of Sensitizing Reaction

Treatment	Potentially sensitized			Percentage sensitized (%)
	no	yes	total	
Test	186	43	229	18.78
Reference	185	43	228	18.86

The primary analysis of sensitization used the PPPS and compared the number and percentage of sensitization reactions (irritation score greater than or equal to 2 at 48 or 72 hours post removal) observed with each patch type (see Table 9).

Table 10 presents the 95% UCL for the difference in proportions of potentially sensitized patients for the test versus reference, using the Sensitization Per-Protocol Population (PPPS). Based on the 95% UCL for the difference in proportions, the test may exceed the reference by at most 1.3 percentage points with regard to the proportion of subjects who had sensitization.

Table 10: Confidence bound based on the numbers of subjects with potentially sensitized scores

Test patch potentially sensitized and reference patch not potentially sensitized (P_T)	Test patch not potentially sensitized and reference patch potentially sensitized (P_R)	Total N	$p_T - p_R$	One-sided 95% Upper Bound *	
				McNemar	Clopper
0	0	228	0	0.0044	0.0131

* 95% UCL for $p_T - p_R$, where p_T = potentially sensitized for test product, and p_R = potentially sensitized for reference product

3.3 Evaluation of Adhesion

3.3.1 Study design and endpoints

Study Objective

The objective of this study was to assess adhesion of Rivastigmine 9.5 mg/24 hours Patch (Transdermal System) compared to that of Exelon 9.5 mg/24 hours Patch (Rivastigmine Transdermal System) following a 24-hour application period in healthy adult subjects.

Study design

This was a randomized, single-dose, 2-period, 2-treatment, open-label crossover adhesion study. A total of 30 healthy adult subjects (male and female) were enrolled in the study. On Day 1 and Day 8, each subject received either a single patch application of the test product, Rivastigmine Transdermal System, 9.5 mg/24 hours, or a single patch application of the reference product, Exelon Patch, 9.5 mg/24 hours, to the upper back as per the randomization. The patches were worn for a period of 24 hours. Taping or any external reinforcement of the patches was not allowed throughout the conduct of the study. Patch adhesion was evaluated at 0 (immediately following patch application), 2, 4, 6, 8, 10, 12, 18, and 24 hours ($\pm$ 10 minutes) after patch application.

Treatments

Treatment consisted of the following:

Treatment	Description
Test (A)	Rivastigmine Transdermal System, 9.5 mg/24 hours*
Reference (B)	Exelon® Patch, 9.5 mg/24 hours**

* Patch manufactured by (b) (4) (Lot No. C0004AL0AU); **Patch manufactured by LTS Lohmann Therapy Systems Corp.

Adhesion evaluations

0	90% or more adhered (essentially no lift off of the skin)
1	75% to <90% adhered (some edges only lifting off of the skin)
2	50% to <75% adhered (less than half of the system lifting off the skin)
3	<50% adhered but not detached (more than half the system lifting off of the skin but not detached)
4	0% adhered-Patch detached (patch completely off the skin)

Clinical endpoints

Primary endpoint: Mean Cumulative Adhesion Scores

The mean cumulative adhesion scores per subject were obtained by adding the scores at 0, 2, 4, 6, 8, 10, 12, 18, and 24 hours of the application period and dividing by the number of observations.

Secondary endpoints: The clinical reviewer requested a comparison of the difference between test and reference with regard to the proportion of patch applications with meaningful detachment. Two dichotomized endpoints, defined as 1) greater than or equal to a score of 1 ($\geq 10\%$ detached) and 2) greater than or equal to a score of 2 ($\geq 25\%$ detached), were analyzed for the mean cumulative adhesion scores and adhesion scores at 0, 2, 4, 6, 8, 10, 12, 18, and 24 hours.

3.3.2 Subject disposition

A total of 30 healthy adult subjects entered into this study and 27 were included in the sponsor's Per-Protocol Population for adhesion (PPPA) analysis.

3.3.3 Results and conclusions

3.3.3.1 Sponsor's analysis results

Summary of Cumulative Adhesion Score – PPPA (Clinical Study report Cetero R10-1307, P49, Table 11.4.2)

	Test Product A: Rivastigmine Transdermal System, 9.5 mg/24 hours	Reference Product B: Exelon Patch, 9.5 mg/24 hours
N	27	27
Arithmetic Mean	0.70	0.52
Standard Deviation	1.49	1.05
Median	0.00	0.00
Max	0.00	0.00
Min	6.00	4.00

To demonstrate non-inferiority of test product A, Rivastigmine Transdermal System, 9.5 mg/24 hours, compared to reference product B, Exelon Patch, 9.5 mg/24 hours, with regard to the cumulative adhesion score (CAS), the scores for reference product B were first scaled by multiplying the individual total CAS by 1.25. The pairwise difference between the test and scaled reference CAS was then computed for each subject. Bootstrap simulations (10,000 datasets) were then performed using sampling with replacement. The bootstrap median for each dataset was calculated and an overall 95% UCL was constructed based on the ranked medians.

The 95% bootstrap UCL of the median difference between the test product A and reference product B is shown in the table below.

**Summary of 95% Bootstrapping Confidence Limit -- CAS (PPPA – N=27)
(Clinical Study report Cetero R10-1307, P50, Table 11.4.4)**

Variable	Median Difference	Upper Bound of 95% Bootstrap Confidence Limit of the Median Difference
Cumulative Adhesion Scores (Test – 1.25*Reference)	0.00	0.00

The 95% UCL was equal to zero, which indicates that test product A, Rivastigmine Transdermal System, 9.5 mg/24 hours, was non-inferior to the reference product B, Exelon Patch, 9.5 mg/24 hours.

Given the paired nature of data, the Wilcoxon Signed Rank Test was also used to assess the statistical significance in the difference between the CAS of the test product A, Rivastigmine Transdermal System, 9.5 mg/24 hours, and the scaled CAS of reference product B, Exelon Patch, 9.5 mg/24 hours. The table below summarizes the results of the adhesion analysis using the CAS as the response variable and the Wilcoxon Signed Rank Test.

Statistical Results of Adhesion Analysis Using Wilcoxon Signed Rank Test – CAS (PPPA – N=27) Clinical Study report Cetero R10-1307, P50, Table 11.4.5)

Variable	Hypotheses	Test Statistic	<i>p</i> -value
Cumulative Adhesion Scores (Test – 1.25*Reference)	H ₀ : Median _T – 1.25Median _R > 0 H ₁ : Median _T – 1.25Median _R ≤ 0	-149.5	0.2004

3.3.3.2 FDA Reviewer’s Results

The analysis is based on Per Protocol Population for Adhesion (PPPA).

For some subjects, the evaluation score was 1 at an earlier visit and 0 at subsequent visit(s). In these cases we used the LOCF for later visits.

Table 11 shows the frequency of cumulative adhesion scores per each patch at each evaluation time using LOCF data.

Table 11. Frequency of adhesion scores (PPPA) using LOCF data

Treatment	Score	Hour 0	Hour 2	Hour 4	Hour 6	Hour 8	Hour 10	Hour 12	Hour 18	Hour 24
Test	0	27 (100.00%)	27 (100.00%)	27 (100.00%)	27 (100.00%)	25 (92.59%)	24 (88.89%)	22 (81.48%)	20 (74.07%)	20 (74.07%)
	1	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.41%)	3 (11.11%)	5 (18.52%)	7 (25.93%)	6 (22.22%)
	2	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)
	3	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	4	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Reference	0	27 (100.00%)	27 (100.00%)	27 (100.00%)	27 (100.00%)	26 (96.30%)	24 (88.89%)	24 (88.89%)	21 (77.78%)	20 (74.07%)
	1	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	3 (11.11%)	3 (11.11%)	6 (22.22%)	7 (25.93%)
	2	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	3	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	4	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Table 12. Waiver Analysis for Test and the RLD

Product	Visit	Percentage of Patches with Score=0	Average
Test	Hour 0	27/27 = 100%	90.1%
	Hour 2	27/27 = 100%	
	Hour 4	27/27 = 100%	
	Hour 6	27/27 = 100%	
	Hour 8	25/27 = 92.6%	
	Hour 10	24/27 = 88.9%	
	Hour 12	22/27 = 81.5%	
	Hour 18	20/27 = 74.1%	
Reference	Hour 24	20/27 = 74.1%	91.8%
	Hour 0	27/27 = 100%	
	Hour 2	27/27 = 100%	
	Hour 4	27/27 = 100%	
	Hour 6	27/27 = 100%	
	Hour 8	26/27 = 96.3%	
	Hour 10	24/27 = 88.9%	
	Hour 12	24/27 = 88.9%	
Hour 18	21/27 = 74.1%		
Hour 24	20/27 = 77.8%		

Table 12 shows-the test and reference products meet the adhesion criterion of 90/90 ($\geq 90\%$ of patches having $\geq 90\%$ adhesion throughout the entire study). Based on “Memo for Statistical Non-inferiority Analysis for Highly Adhering Patch Drug Products”, the adhesion study should be permitted to waive the requirement of passing the NI statistical test- since meeting those conditions is sufficient evidence for demonstrating high adhesion.

4 Summary and Conclusions

4.1 Statistical Issue and Findings

Irritation and sensitization study #C10-1870

Irritation

Primary endpoint: The mean cumulative irritation scores for the test and reference groups were 1.52 and 1.55 respectively. The non-inferiority criterion was satisfied for test versus reference, therefore we can conclude that the population mean of the mean cumulative irritation score for the test patch does not exceed that of the reference patch by more than 25% (i.e. $\mu_T / \mu_R \leq 1.25$).

Secondary endpoints: Dichotomized endpoints for the mean cumulative irritation scores were considered for the secondary analyses. Based on the 95% UCL for the difference in proportions, the test product proportion of subjects with mean cumulative irritation scores >1 might exceed that of the reference product by at most 2.4 percentage points. The test product might exceed the reference product by at most 3.0 percentage points with regard to the proportion of subjects who had mean cumulative irritation scores greater than 2.

Also, the test and reference patches were compared with regard to the proportion of patch applications with irritation scores of 1 or greater for each study day. The test product might exceed the reference product by at most 3.6, 2.1, and 1.7 percentage points for Days 8, 15, and 22 respectively. The test and reference patches were compared with regard to the proportion of patch applications with irritation scores of 2 or greater. The test product might exceed the reference product by at most 4.5, 2.2, and 2.5 percentage points for Days 8, 15, and 22 respectively.

Sensitization

It was the decision of the clinical reviewer not to request a re-challenge phase since the one subject ^{(b) (6)} that was not sensitized to both the test and reference products was sensitized to the reference product.

The test patch might exceed the reference patch by at most 1.3 percentage points based on the 95% UCL for the difference in sensitization rates.

Adhesion study #R10-1307

The test and reference product met the adhesion criterion of 90/90 ($\geq 90\%$ of patches having $\geq 90\%$ adhesion throughout the entire study). Based on the memo for statistical non-inferiority analysis for highly adhering patch drug products, the adhesion study should be permitted to waive the requirement of passing the NI statistical test, since meeting those conditions is sufficient evidence for demonstration high adhesion. One concern is that the adhesion study had 27 subjects rather than the memo recommended minimum of 60 subjects.

Main difference between sponsor's results and FDA's results:

The following is a list of differences between the results.

- a) For the non-inferiority irritation analyses, the sponsor provided a 95% UCL for the difference ($\mu_T - 1.25\mu_R$) based on the cumulative irritation scores; the sample size was 262 (PPPI). The FDA calculated the 95% UCL for the mean difference ($\mu_T - 1.25\mu_R$) based on the mean cumulative irritation scores; the sample size was 260 (FDA PPPI).

- b) The sponsor provided a non-inferiority test for the sensitization analysis. The 95% UCL for ($\mu_T - 1.25\mu_R$) was less than zero, which demonstrated that test product is non-inferior to the reference product. The FDA conducted the primary analysis of the sensitization study using the PPPS, and compared the number and percentage of sensitization reactions (irritation score greater than or equal to 2 at 48 or 72 hours post removal) observed with each patch type. Based on the 95% UCL for the difference in proportions, the test can exceed the reference by at most 1.3 percentage points with regard to the proportion of subjects who had sensitization.

- c) The sponsor provided non-parametric analyses using the Wilcoxon Signed Rank Test and a bootstrap method for median difference. The analyses demonstrated that the test product was not statistically different to that of the scaled reference product. The FDA concluded that the adhesion study passed the adhesion waiver, based on the memo "Waiver of Statistical Non-Inferiority Analysis for Highly Adhering Patch Drug Products, February 10, 2014."

4.2 Conclusions

The test patch was found to be non-inferior to the reference patch for irritation and sensitization, and both the test and reference patches passed the adhesion waiver.

Guoying Sun, Ph.D.
Mathematical Statistician, DB6/OB

Stella C. Grosser, Ph.D.
Team Leader, DB6/OB

cc:

HFD-600 Nitin K Patel

HFD-705 Stella C. Grosser, Guoying Sun

HFD-700 Lillian Patrician OB

5 References

Joseph L. Fleiss, Bruce Levin, and MyungHee Cho Paik. (1981). *Statistical Methods for Rates and Proportions* (2nd edition). New York: Wiley-Interscience.

McNemar, Q. (1947). Note on the sampling error of the difference between correlated proportions or percentages. *Psychometrika*, 12, 153-157.

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Waiver of Statistical Non-Inferiority Analysis for Highly Adhering Patch Drug Products, February 10, 2014.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GUOYING SUN
05/23/2014

VICKI A LANCASTER
05/28/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 204403

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE

ANDA No.	204403
Drug Product Name	Rivastigmine Transdermal System
Strength(s)	4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr
Applicant Name	Alvogen Pine Brook, Inc.
Original Submission Date(s)	June 12, 2012
Submission Date(s) of OSI Inspection Report	March 4, 2011
Reviewer	Tiffany Pokora, PharmD
Clinical Site	Cetero Research
Clinical Site Address	4801 Amber Valley Parkway Fargo, ND 58104, USA
Analytical Site	(b) (4)
Analytical Site Address	(b) (4)
OUTCOME DECISION	ADEQUATE

EXECUTIVE SUMMARY

This is a review to finalize the bioequivalence portion of the application. The firm has accepted the FDA-recommended dissolution method and specification. No Office of Scientific Investigations (OSI) inspection is pending or necessary for the clinical and analytical sites. The sites have been found to be acceptable by the reviewer in the original bioequivalence review. The bioequivalence section of the application is complete.

OSI COMMENTS:

A routine inspection of the Clinical site, Cetero Research, (4801 Amber Valley Parkway, Fargo, ND 58104) was requested for NDA 203202 on 10/28/2011 and was completed on 12/15/2011 with an outcome of NAI.

OSI Inspection History: A Routine inspection of the Analytical site, (b) (4) was requested for (b) (4) on 4/8/2009 and was completed on (b) (4) with an outcome of VAI.

Per the OSI inspection report review for (b) (4), the findings of the OSI inspection were specific to the parent ANDA and, therefore, will not affect the studies in ANDA 204403. ANDA 204403 is now adequate.

From: Miller, Jennifer
Sent: Thursday, December 18, 2014 8:19 PM
To: Pokora, Tiffany
Subject: RE: ANDA 204403: OSI for Analytical Site

Hi Tiffany,

Per the OSI inspection report review, the findings of the OSI inspection were specific to the parent ANDA and, therefore, will not affect the studies in ANDA 204403. ANDA 204403 is now adequate.

Thanks,
Jen

From: Pokora, Tiffany
Sent: Thursday, December 18, 2014 9:33 AM
To: Miller, Jennifer
Subject: ANDA 204403: OSI for Analytical Site

Hi Jennifer,

You completed the Bioequivalence review for ANDA 204403 on 2/7/2014 (see attachment) and found the review Inadequate, pending an OSI inspection of the analytical site. This ANDA has become a priority for the Office. As such, I looked into the analytical site to see if we can close it out and found an applicable inspection within our 3.5 year study date window for (b) (4) with an outcome of VAI.

I've attached the DB review of the OSI inspection report for this ANDA. Can you please review this to see if the inspection is acceptable for ANDA 204403? If so, please send me an email confirming this and I will close out the Bioequivalence review.

Thank you in advance for your help with this.

Kind regards,

Tiffany Pokora, Pharm.D.
Project Manager, Division of Bioequivalence II
FDA | CDER | OGD | DBII

RECOMMENDATIONS:

From a bioequivalence point of view, the firm has met the requirements for in-vivo bioequivalence. The bioequivalence section of the application is acceptable and we have no further questions at this time.

BIOEQUIVALENCE COMMENT

ANDA: 204403
APPLICANT: Alvogen Pine Brook, Inc.
DRUG PRODUCT: Rivastigmine Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr,
and 13.3 mg/24 hr

The Division of Bioequivalence II (DBII) has completed its review of your submission acknowledged on the coversheet and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are comprehensive as of issuance. These comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

COMPLETED ASSIGNMENT FOR 204403 ID: 25007

Reviewer: Pokora, Tiffany

Date Completed: 12/19/2014

Verifier: Nhu, Diane

Date Verified: 12/19/2014

Division: Division of Bioequivalence

Description: PM Acceptable OSI Closeout Review

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
25007	12/19/2014	Other (REGULAR)	OSI Inspection Report PMs	1	1
				Total:	1

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	204403		
Drug Product Name	Rivastigmine Transdermal System		
Strength(s)	4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr		
Applicant Name	Alvogen Pine Brook, Inc.		
Address	10 Bloomfield Avenue Building B Pine Brook, NJ 07058		
Applicant's Point of Contact	Jasmin Shah		
Contact's Telephone Number	(b) (6)		
Contact's Fax Number	973.201.1086		
Original Submission Date(s)	June 12, 2012		
Submission Date(s) of Amendment(s) Under Review	January 22, 2013 (New strength amendment – 13.3 mg/24 hr) December 27, 2013 (ECD Response – COA of RLD)		
Reviewer	Jennifer N. Miller, Ph.D.		
Study Number (s)	R10-1307		
Study Type (s)	Fasting		
Strength (s)	9.5 mg/24 hours		
Clinical Site	Cetero Research		
Clinical Site Address	4801 Amber Valley Parkway Fargo, ND 58104, USA		
Analytical Site	(b) (4)		
Analytical Site Address			
OVERALL REVIEW RESULT	INADEQUATE		
WAIVER REQUESTS	ADEQUATE		
OSI REPORT RESULT	INADEQUATE (Pending an OSI inspection of the analytical site.)		
Dissolution Review Results	Dissolution was reviewed in separate documents (DARRTS REV-BIOEQ-02(Dissolution Review); Submit Dates: 3/23/13, 5/17/13, 9/13/13, 9/24/13, and 12/19/13). Please refer to these reviews for dissolution history and deficiencies.		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	STUDY/TEST TYPE	STRENGTH	REVIEW RESULT
0, 15	FASTING STUDY	9.5 mg/24 hr	ADEQUATE
0, 15	WAIVERS	4.6 mg/24 hr and 13.3 mg/24 hr	ADEQUATE

1 EXECUTIVE SUMMARY

This application contains the results of a fasting bioequivalence (BE) study comparing a test product, Alvogen Pine Brook, Inc.'s Rivastigmine Transdermal System, 9.5 mg/ 24 hours, to the corresponding reference product, Novartis' Exelon® Patch, 9.5 mg/24 hours. The BE study was designed as a single-dose, two-way crossover study in healthy male and female subjects. The firm's fasting BE study is acceptable. The results are summarized in the tables below.

Rivastigmine Transdermal System, 9.5 mg/24 hours Fasting Bioequivalence Study No. R10-1307, N=27 (Male=8 and Female=19) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (pg·hr/mL)	163479.0	143870.9	1.14	106.61	121.11
AUC _∞ (pg·hr/mL)	164348.9	144818.8	1.13	106.51	120.92
C _{max} (pg/mL)	9067.37	7869.17	1.15	107.05	124.02

Per dissolution review, the firm's dissolution testing is inadequate pending the firm's acknowledgment of the FDA-recommended method and specification for its product (see DARRTS REV BIOEQ-02(Dissolution Review); Submit Dates: 3/23/13, 5/17/2013, 9/13/13, 9/24/13, and 12/19/13 for dissolution history and deficiencies). The firm's response to dissolution deficiencies will be reviewed separately.

The DB II deems the 4.6 mg/24 hours and 13.3 mg/24 hours strengths bioequivalent based on criteria set forth in 21 CFR § 320.24 (b) (6).

A routine inspection of the Clinical site, Cetero Research, (4801 Amber Valley Parkway, Fargo, ND 58104) was requested for NDA 203202 on 10/28/2011 and was completed on 12/15/2011 with an outcome of NAI.

A for cause inspection of the Analytical site, (b) (4) was requested for ANDA 200920 on 3/21/2013 and is **pending**.

The application is **inadequate**, pending the OSI inspection of the Analytical site.

NOTE: The application contains the results of three studies, (1) a Bioequivalence (BE) study (#R10-1307) on the 9.5 mg/24 hours strength, (2) Adhesion study (#R10-1307) on the 9.5 mg/24 hours strength, and (3) Sensitization/Irritation study [#C10-1870 (R10-1318, S11-0069)] on the 4.6 mg/24 hours strength. The Division of Bioequivalence (DB) II will review the bioequivalence study, and the Division of Clinical Review (DCR) will review the Adhesion and Sensitization/Irritation studies.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Rivastigmine Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr
Reference Product	Exelon® Patch
RLD Manufacturer	Novartis
NDA No.	022083
RLD Approval Date	4.6 mg/24 hr and 9.5 mg/24 hr: July 6, 2007 13.3 mg/24 hr: August 31, 2012
Indication	Exelon Patch is an acetylcholinesterase inhibitor indicated for treatment of: • Mild, moderate, (b)(4) dementia of the Alzheimer’s type. • Mild to moderate dementia associated with Parkinson’s disease.

3.2 PK/PD Information

Bioavailability	After the initial application of Exelon Patch, there is a lag time of 0.5 to 1 hour in the absorption of rivastigmine. Concentrations then rise slowly typically reaching a maximum after 8 hours, although maximum values (Cmax) can also occur later (at 10 to 16 hours). After the peak, plasma concentrations slowly decrease over the remainder of the 24-hour period of application. At steady state, trough levels are approximately 60 to 80% of peak levels. Exelon Patch 9.5 mg/24 hours gave exposure approximately the same as that provided by an oral dose of 6 mg twice daily (i.e., 12 mg/day). Inter-subject variability in exposure was lower (43% to 49%) for the Exelon Patch formulation as compared with the oral formulations (73% to 103%). Fluctuation (between Cmax and Cmin) is less for Exelon Patch than for the oral formulation of rivastigmine. Over a 24-hour dermal application, approximately 50% of the drug content of the patch is released from the system. Exposure (AUC∞) to rivastigmine (and metabolite NAP266-90) was highest when the patch was applied to the upper back, chest, or upper arm. Two other sites (abdomen and thigh) could be used if none of the 3 other sites is available, but the practitioner should be aware that the rivastigmine plasma exposure associated with these sites was approximately 20% to 30% lower. There was no relevant accumulation of rivastigmine or the metabolite NAP226-90 in plasma in patients with Alzheimer’s disease with daily dosing. The pharmacokinetic profile of rivastigmine transdermal patches was comparable in patients with Alzheimer’s disease and in patients with

	dementia associated with Parkinson’s disease
Food Effect	N/A
Tmax	8 hours
Metabolism	Rivastigmine is extensively metabolized primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite NAP226-90. <i>In vitro</i>, this metabolite shows minimal inhibition of acetylcholinesterase (<10%). Based on evidence from <i>in vitro</i> and animal studies, the major cytochrome P450 isoenzymes are minimally involved in rivastigmine metabolism. The metabolite-to-parent AUC_∞ ratio was about 0.7 after Exelon Patch application versus 3.5 after oral administration, indicating that much less metabolism occurred after dermal treatment. Less NAP226-90 is formed following patch application, presumably because of the lack of presystemic (hepatic first pass) metabolism. Based on <i>in vitro</i> studies, no unique metabolic routes were detected in human skin.
Excretion	Renal excretion of the metabolites is the major route of elimination. Unchanged rivastigmine is found in trace amounts in the urine. Following administration of 14C-rivastigmine, renal elimination was rapid and essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the feces. Renal clearance was approximately 2.1 to 2.8 L/hr.
Half-life	3 hours
Drug Specific Issues (if any)	None.
Dosage and Administration	- Apply patch on intact skin for a 24-hour period; replace with a new patch every 24 hours Initiate treatment with 4.6 mg/24 hours Exelon Patch After a minimum of 4 weeks, if tolerated, increase dose to 9.5 mg/24 hours, which is the minimum effective dose Following a minimum additional 4 weeks, may increase dosage to maximum dosage of 13.3 mg/24 hours Mild to Moderate Alzheimer’s Disease and Parkinson’s Disease Dementia: Exelon Patch 9.5 mg/24 hours or 13.3 mg/24 hours once daily (b) (4) Alzheimer’s Disease: Exelon Patch 13.3 mg/24 hours once daily - For treatment interruption longer than 3 days, retitrate dosage starting at 4.6 mg/24 hours

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2

1.	Type of study:	Bioequivalence (BE) with Pharmacokinetic (PK) Endpoints and Adhesion Study
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	9.5 mg/24 hr
	Subjects:	Healthy males and nonpregnant females, general population
	Additional Comments:	The transdermal patch should be applied to clean, dry, hairless, intact

		healthy skin on the upper back, chest, or upper arm, as recommended in the approved reference listed drug (RLD) labeling and worn for 24 hours.

2.	Type of study:	Skin Irritation and Sensitization Study
	Design:	Randomized, evaluator-blinded, in vivo, within-subject repeat test
	Strength:	4.6 mg/24 hr (Dose: One-half of 4.6 mg/24 hr patch)
	Subjects:	Healthy males and nonpregnant females, general population.
	Additional Comments:	See guidance at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201278.pdf

Analytes to measure (in plasma/serum/blood):	Rivastigmine in plasma
Bioequivalence based on:	Rivastigmine
Waiver request of in-vivo testing:	4.6 mg/24 hours and 13.3 mg/24 hours
Source of most recent recommendations:	Individual Draft Guidance on Rivastigmine Extended Release Film: http://www.fda.gov/cder/guidance/bioequivalence/default.htm (Recommended Feb 2010; Revised Jun 2010, Nov 2010, Nov 2013) Per DB's most recent control correspondence # 12-0937¹, 9.5 mg/24 hr strength remains as the RLD for this product, the new added highest strength of 13.3 mg/24 hrs may also be deemed to be bioequivalent to 9.5 mg/24 hr strengths of Exelon based on (i) acceptable bioequivalence studies on the 9.5mg/24 hr strength, (ii) acceptable dissolution testing of all strengths, and (iii) proportional similarity in the formulations across all strengths. Control #12-0937: \\cdsnas\OGDS6\CONTROLS\2012-docs\12-0937.pdf
Summary of OGD or DB History (for details, see Appendix 4.4):	See Appendix 4.4

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose Fasting Bioequivalence (BE) with Pharmacokinetic (PK) Endpoints and Adhesion Study	Yes	1

¹ V:\FIRMSAM\Amneal\CONTROLS\120937C1012 addendum.doc

Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	Yes	3
Waiver requests	Yes	2
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	No	--

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	5.3.1.4
Analyte	Rivastigmine
Internal standard (IS)	Rivastigmine-d6
Method description	Solid phase extraction procedure
Limit of quantitation	LLOQ 100.0 pg/mL
Average recovery of drug (%)	LQC: 83.4% MQC: 84.4% HQC: 81.5% Mean: 83.1%
Average recovery of IS (%)	82.7%
Standard curve concentrations (units/mL)	100.0, 200.0, 500.0, 1000, 2000, 4000, 8000 and 10000 pg/mL
QC concentrations (units/mL)	LLOQ 100.0 pg/mL LQC 300.0 pg/mL MQC 3000 pg/mL HQC 7500 pg/mL ULOQ 10000 pg/mL
QC Intraday precision range (%)	LLOQ 5.3 to 13.2% LQC 2.3 to 6.4% MQC 1.8 to 4.1% HQC 1.3 to 2.7% ULOQ 2.2 to 2.8%
QC Intraday accuracy range (%)	LLOQ 0.6 to 13.4% LQC -2.1 to 5.7% MQC 1.4 to 4.0% HQC -0.3 to 0.1% ULOQ 3.1 to 4.4%
QC Interday precision range (%)	1.9 to 10.8%
QC Interday accuracy range (%)	-0.1 to 5.5%
Bench-top stability (hrs)	24 hours @ room temperature
Stock stability (days)	25 days @ room temperature and 4°C ± 6°C for drug 14 days @ room temperature for internal standard 44 days @ 4°C ± 6°C for internal standard

Processed stability (hrs)	24 hours @ room temperature 94 hours @ 5°C ± 3°C
Freeze-thaw stability (cycles)	6 cycles
Long-term storage stability (days)	54 days @ -20°C ± 10°C and -70°C ± 20°C
Dilution integrity	Dilution integrity 50000 pg/mL and diluted high QC 7500 pg/mL, both diluted 10 times
Selectivity	There were no significant interfering peaks in the blank plasma samples at the retention time of rivastigmine or the internal standard as seen in the chromatograms.

SOPs submitted	Yes	SOP (b) (4) "Quantitative Bioanalytical Method Validation" (Effective Date: (b) (4) (b) (4) and SOP (b) (4) "Assay Validation in Biological Fluids" (Effective Date: (b) (4) (b) (4))
Bioanalytical method is acceptable	Yes	

Comments on the Pre-Study Method Validation:

The firm also submitted adequate data for a partial validation to transfer the method from Cetero Research, Fargo, ND, USA (AP LC/MS/MS 204.2) to (b) (4) (b) (4)

Human plasma containing K₂EDTA was used for preparation of all calibration standards and quality control samples. The pre-study method validation is **adequate**.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments: Dose, Dosage Form, Route, Product ID	Subjects ¹ No. (M/F) Type Age: Mean (Range)	Arithmetic Mean (%CV) Pharmacokinetic Parameters ¹						Study Report Location
					Median (Range) for T _{max}						
					C _{max} (pg/mL)	T _{max} (hr)	AUC _{0-t} (pg-hr/mL)	AUC _{0-inf} (pg-hr/mL)	T _{1/2} (hr)	Kel (1/hr)	
R10-1307	Assess the relative bioavailability and adhesion of Rivastigmine 9.5 mg / 24 hour Patch compared to that of Exelon 9.5 mg / 24 hour patch following a 24 hour application period in healthy adult subjects.	Randomized, single-dose, 2-way open-label crossover bioavailability and adhesion study	Test: Rivastigmine Transdermal System 9.5 mg / 24 hours, Transdermal, Batch No. C0004AL0AU	27 (8/19) Healthy Volunteers 44.4 yr (19 - 63)	9529.04 (32.05)	10.00 (8.00–24.00)	170277.10 (28.64)	171122.71 (28.53)	2.50 (17.28)	0.2857 (17.98)	Module 5.3.1.2, study r10-1307, r10-1307, report-body.pdf
			Reference: Exelon Patch 9.5 mg / 24 hours, Transdermal,; Lot No. 1401B		8355.33 (39.52)	10.00 (4.00–26.00)	151364.07 (35.07)	152267.31 (34.91)	2.56 (11.85)	0.2746 (11.56)	

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Rivastigmine Transdermal System, 9.5 mg/24 hours					
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. R10-1307)					
Parameter	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	163479.0	143870.9	1.14	106.61	121.11
AUC _∞ (hr *pg/ml)	164348.9	144818.8	1.13	106.51	120.92
C _{max} (pg/ml)	9067.37	7869.17	1.15	107.05	124.02

Table 3. Reanalysis of Study Samples

Study No. R10-1307								
Additional information in Sample Analysis Report, Volume(s), Page(s) 14-17								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Above limit of quantitation	63.00	34.00	5.07	2.74	63.00	34.00	5.07	2.74
Data acquisition malfunction	0.00	1.00	0.00	0.08	0.00	1.00	0.00	0.08
Low internal standard	0.00	1.00	0.00	0.08	0.00	1.00	0.00	0.08
Total	63.00	36.00	5.07	2.90	63.00	36.00	5.07	2.90

Did use of recalculated plasma concentration data change study outcome? N/A

Comments from the Reviewer:

No samples in the fasting BE study were reanalyzed for apparent pharmacokinetic reasons. All samples were repeated according to (b) (4) “Sample Reanalysis and Reporting Criteria” (effective (b) (4)).

3.7 Formulation

Location in appendix	Section 4.2, Page 28
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	FORMULATION ACCEPTABLE
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DB Dissolution Review	REV-BIOEQ-02(Dissolution Review) Submit Dates: 3/23/13, 5/17/13, 9/13/13, 9/24/13, and 12/19/13
Source of Method (USP, FDA or Firm)	FDA
Medium	0.9% NaCl @ 32°C
Volume (mL)	500 mL
USP Apparatus type	Modified USP Type VI (Cylinder)
Rotation (rpm)	50 rpm
DB-recommended specifications	1 hr: (b) (4) 2 hr: 4 hr: 9 hr: 24 hr
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	Yes
If no, reason why F2 not calculated	
Is method acceptable?	METHOD INCOMPLETE
If not then why?	Dissolution was reviewed in separate documents (DARRTS REV-BIOEQ-02(Dissolution Review); Submit Dates: 3/23/13, 5/17/13, 9/13/13, 9/24/13, and 12/19/13). Please refer to these reviews for dissolution history and deficiencies. Pending the firm's acceptance of the FDA-recommended method and specifications.

F2 metric, biostudy strengths compared to other strength(s)			
Biostudy Strength	Other Strength	F2 metric for test	F2 metric for RLD
9.5 mg/24 hr	4.6 mg/24 hr	93.19	87.00
9.5 mg/24 hr	13.3 mg/24 hr	82.57	98.83

F2: Multi media dissolution testing using (b) (4) of medium and Modified USP
 (b) (4) (4.6 mg/24hr, 9.5 mg/24hr)



F2: Multimedia dissolution testing using 500 mL medium and modified USP Apparatus Type VI at 50 rpm (4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr patches)

F2 metric, Multi-Media (HCl Buffer, pH 1.2)			
Biostudy Strength	Other Strength	F2 metric for T vs T	F2 metric for T vs R
9.5 mg/24 hr	4.6 mg/24 hr	83.39	81.39
9.5 mg/24 hr	13.3 mg/24 hr	85.31	84.24
F2 metric, Multi-Media (Acetate Buffer, pH 4.5)			
Biostudy Strength	Other Strength	F2 metric for T vs T	F2 metric for T vs R
9.5 mg/24 hr	4.6 mg/24 hr	90.11	76.26
9.5 mg/24 hr	13.3 mg/24 hr	77.94	77.42
F2 metric, Multi-Media (Phosphate Buffer, pH 6.8)			
Biostudy Strength	Other Strength	F2 metric for T vs T	F2 metric for T vs R
9.5 mg/24 hr	4.6 mg/24 hr	87.87	82.93
9.5 mg/24 hr	13.3 mg/24 hr	75.31	96.08

3.9 Waiver Requests

Strengths for which waivers are requested	4.6 mg/24 hours and 13.3 mg/24 hours
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	No
Waivers granted?	Deemed Bioequivalent
If not then why?	

3.10 Deficiency Comments

None.

3.11 Recommendations

1. The Division of Bioequivalence (DB) II accepts the fasting BE study (10-1307) conducted by Alvogen Pine Brook Inc. on its Rivastigmine Transdermal System, 9.5 mg/ 24 hours, Lot #C0004AL0AU, comparing it to the corresponding reference product, Novartis' Exelon® Patch, 9.5 mg/24 hours, Lot #1401B.
2. The formulations of the 4.6 mg/24 hours and 13.3 mg/24 hours strengths are proportionally similar to the 9.5 mg/24 hours strength of the test product which underwent bioequivalence testing. The DB II deems the 4.6 mg/24 hours and 13.3 mg/24 hours strengths bioequivalent based on criteria set forth in 21 CFR § 320.24 (b) (6).

The application is **inadequate**, pending the OSI inspection of the analytical site.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
RPM and CSO	Dissolution was reviewed in separate documents (DARRTS REV-BIOEQ-02(Dissolution Review); Submit Dates: 3/23/13, 5/17/13, 9/13/13, 9/24/13, and 12/19/13). Please refer to these reviews for dissolution history and deficiencies.
CMC	The backing liner (b) (4) of the 13.3 mg/24 hour strength is proposed at a level of (b) (4) which exceeds the maximum level in the IIG Database. However, the liner should not be applied to the patients' skin as it's designed to protect the patch form the environment and discarded before the patch is placed on the skin. Therefore, from a Bioequivalence perspective, the amount of backing liner used in this product is acceptable.
ALL	A for cause inspection of the Analytical site, (b) (4) (b) (4) was requested for ANDA 200920 on 3/21/2013 and is pending .

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	R10-1307			
Study Title	A Study to Evaluate the Relative Bioavailability and Adhesive Properties of Rivastigmine 9.5 mg / 24 Hours Patch (Transdermal System) Versus Exelon 9.5 mg / 24 Hours Patch (Transdermal System) In Normal Healthy Volunteers			
Study Type	☒ In Vivo Be	☐ In Vitro BE	☐ Permeability	☒ Other (Specify) Adhesion
Study Report Location:				
Study Report	5.3.1.2			
Validation Report	5.3.1.4			
Bioanalytical Report	5.3.1.4			
Clinical Site (Name, Address, Phone #)	Cetero Research 4801 Amber Valley Parkway Fargo, ND 58104, USA (701) 239-4750			
Principal Investigator	Anthony R. Godfrey, PharmD anthony.godfrey@cetero.com			
Dosing Dates	Period I:	12 November 2011		
	Period II:	19 November 2011		
Analytical Site (Name, Address, Phone #)	(b) (4)			
Analysis Dates	First extraction: 02-Dec-2011 Last injection: 11-Dec-2011			
Analytical Director	(b) (4)			
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	Twenty-eight (28) days from the first sample collected on 12-Nov-2011 to the last sample extracted on 10-Dec-2011.			

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Rivastigmine Transdermal System, 9.5 mg/24 hours	Exelon Patch, 9.5 mg/24 hours
Manufacturer	(b) (4)	LTS Lohmann Therapy Systems Corp.
Batch/Lot No.	C0004AL0AU	1401B
Manufacture Date	27 Jun 2011	N/A
Expiration Date	Dec 2011	Jan 2013
Strength	9.5 mg/24 hours	9.5 mg/24 hours
Dosage Form	Transdermal System	Transdermal System
Bio-Batch Size	(b) (4) Patches	N/A
Production Batch Size	(b) (4) Patches	N/A
Potency (Assay)	97.5%	96.64%
Content Uniformity (mean, %CV)	Acceptance Value: 3.2%	N/A
Dose Administered	Topical	Topical
Route of Administration	9.5 mg	9.5 mg

At study check-in for each period, the subjects were reported to the clinical site at least 10 hours prior to day 1 patch application and were required to stay for 36 hours after day 1 patch application. On day 1 (period 1) and day 8 (period 2), each subject received either a single patch application of the test product, 9.5 mg/24 h or a single patch application of the reference product, 9.5 mg/24 h to the upper back following an overnight fast of at least 10 hours. The patches were worn for a period of 24 hours. Taping or any external reinforcement of the patches was not allowed. Following the wash-out period, subjects returned to the clinical facility to be dosed with the alternative treatment to the opposite side of the upper back.

Per Section 9.4.1.2 Patch Application in the Clinical Report, the patch was applied as per the RLD labeling. Patches were applied to clean, dry, intact skin on the upper back and subjects were instructed not to use any creams, lotions, powders, or other products during the study. The patch was firmly pressed into place with the palm of the hand and held for a minimum of 30 seconds.

Patch adhesion was evaluated at 0 (immediately following patch application), 2, 4, 6, 8, 10, 12, 18 and 24 hours after patch application. All 27 subjects who completed the study were analyzed for adhesion. There were no adhesion scores above 2 for either treatment, which indicates that no patches had a significant level of detachment. The DCR will review the Adhesion study.

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 30 Dosed: 30 Completed: 27 Analyzed and included in statistical analysis: 27
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	TR: 2, 3, 6, 7, 11, 12, 15, 16, 17, 19, 23, 24, 25, 27, 30 RT: 1, 4, 5, 8, 9, 10, 13, 14, 18, 20, 21, 22, 26, 28, 29
Blood Sampling Times	Pre-dose and 0.5, 1, 2, 4, 6, 8, 9, 10, 11, 12, 13, 14, 16, 18, 20, 22, 24 (prior to patch removal), 26, 28, 30, 32, and 36 hours.
Blood Volume Collected/Sample	1 x 6 mL in tubes containing K ₂ EDTA
Blood Sample Processing/Storage	Samples were sequentially collected by direct venipuncture in K ₂ EDTA vacutainers, and processed in a timely manner. Samples were gently inverted and cooled by an ice bath immediately after collection until processed, centrifuged at approximately 3000 RPM and 4°C for 10 minutes, and returned to ice. Exactly 1.0 mL of plasma was pipetted into aliquot 1 and aliquot 2. Exactly 10 mcL of the eserine stock solution (see Section 9.5.4.1.1 for preparation of the stock solution) was pipetted into each 1 mL sample of plasma and each sample was then vortexed for 15 seconds. In the event that there was an insufficient volume of plasma to add 1 mL to aliquot 2, the remaining plasma was measured and the appropriate amount of eserine stock solution was added so that the concentration was 1 mcg/1 mL. Samples were then stored and frozen at approximately -70°C ± 10°C until shipment to the bioanalytical laboratory. The time between sample collection and freezer storage did not exceed 1.5 hours.
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	Overnight fast of at least 10 hours.
Length of Confinement	At least 10 hours prior to patch application until at least 36 hours after patch application in each period.

Safety Monitoring	Physical examinations were performed at screening and at study exit. All vital signs throughout the study were measured after a 5 minute rest in a supine position. Blood pressure, heart rate, respiratory rate, and oral temperature were measured at screening. Blood pressure and heart rate were measured prior to patch application (within 90 minutes) and at approximately 12 and 24 hours ($\pm$ 60 minutes) after patch application. Blood pressure, heart rate, and temperature were measured at study exit or early termination. An ECG was recorded at screening. Blood samples were collected at screening, each check-in (females only), and at study exit. Urine samples were collected at screening.

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

R10-1307			
		Treatment Groups	
		Test Product A: Rivastigmine Transdermal System, 9.5 mg / 24 hours N=27 ¹	Reference Product B: Exelon Patch, 9.5 mg / 24 hours N=27 ¹
Age (years)	Mean ± SD	44.4 ± 15.1	44.4 ± 15.1
	Range	19 - 63	19 - 63
Age Groups	< 18	-	-
	18 – 40	8 (29.6%)	8 (29.6%)
	41 – 64	19 (70.4%)	19 (70.4%)
	65 – 75	-	-
	> 75	-	-
Sex	Male	8 (29.6%)	8 (29.6%)
	Female	19 (70.4%)	19 (70.4%)
Hispanic or Latino Race	American Indian or Alaskan Native	-	-
	Asian	-	-
	Black or African American	-	-
	Native Hawaiian or Other Pacific Islander	-	-
	White	-	-
Not Hispanic or Latino Race	American Indian or Alaskan Native	-	-
	Asian	1 (3.7%)	1 (3.7%)
	Black or African American	1 (3.7%)	1 (3.7%)
	Native Hawaiian or Other Pacific Islander	-	-
	White	24 (88.9%)	24 (88.9%)
	White and American Indian or Alaskan Native	1 (3.7%)	1 (3.7%)
BMI	Mean ± SD	24.9 ± 3.0	24.9 ± 3.0
	Range	20.1 - 29.9	20.1 - 29.9

Table 8. Dropout Information, Fasting Bioequivalence Study

R10-1307				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
(b) (6)	Subject elected to withdraw from the study prior to Period I, study hour 11 activities due to AEs (nausea, vomiting, headache). Subject received 1 dose of Test	I	No	NA

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	Product A.			
(b) (6)	Subject elected to withdraw from the study prior to Period I, study hour 9 activities due to an AE (nausea). Subject received 1 dose of Test Product A.	I	No	NA
	Subject elected to withdraw from the study prior to Period I, study hour 10 activities due to AEs (nausea and vomiting). Subject received 1 dose of Reference Product B.	I	No	NA

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Body System/Adverse Event ¹	Reported Incidence by Treatment Groups	
	R10-1307	
	Test Product A: Rivastigmine Transdermal System, 9.5 mg / 24 hours N=29 ²	Reference Product B: Exelon Patch, 9.5 mg / 24 hours N=28 ²
	n (%) ³	n (%) ³
Gastrointestinal disorders		
Abdominal discomfort	1 (3.45%)	1 (3.57%)
Nausea	3 (10.34%)	5 (17.86%)
Vomiting	2 (6.90%)	2 (7.14%)
General disorders and administration site conditions		
Asthenia	-	1 (3.57%)
Metabolism and nutrition disorders		
Decreased appetite	1 (3.45%)	-
Nervous system disorders		
Dizziness	1 (3.45%)	-
Headache	3 (10.34%)	3 (10.71%)
Syncope	-	1 (3.57%)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	-	1 (3.57%)
Total	5 (17.24%)	8 (28.57%)

Table 10. Protocol Deviations, Fasting Bioequivalence Study

R10-1307		
Type	Subject No. Test Product A: Rivastigmine Transdermal System, 9.5 mg / 24 hours	Subject No. Reference Product B: Exelon Patch, 9.5 mg / 24 hours
Concomitant medications	(b) (6)	
Subject (b) (6) reported the use of hormonal IUD but no documentation was provided.		
Period I, check-in staff did not document whether subject had any changes to medical history between screening and check in for Subject (b) (6)		
Period I study hour 14, time of PK collection not documented		
Period II study hour 14, time of PK collection not documented.		
Period II study hour 32, time of PK collection not documented		
Period I, study hour 10, time of PK sample to freezer unknown		
Period II, study hour -11 meal stop time unknown (staff entered stop time of meal as 2046 however meal was served at 2142)		

Comments on Dropouts/Adverse Events/Protocol Deviations:

There were no serious adverse events during the study. Three subjects were dropped from the study. Subject (b) (6) withdrew during Period 1 due to nausea, vomiting and headache. Subject (b) (6) withdrew during Period 1 due to the adverse event of nausea. Subject (b) (6) withdrew during Period 1 due to nausea and vomiting. Three subjects experienced emesis during the study; however, only two subjects were not included in the statistical analysis (Subjects (b) (6) who elected to withdraw from the study). Subject (b) (6) experienced 2 episodes of emesis, 1 during Period I (Day 2 at 1325) and 1 during Period II (Day 1 at 2255). Per the firm's protocol, subjects who experienced emesis were analyzed by the bioanalytical laboratory and used in the PK analysis unless they were removed from the study due to safety concerns. Since this subject was not removed from the study due to safety concerns, the PK data was used in the PK analysis. A summary is provided below:

Subject	T/R	Time of Drug Dosing	Date/Time Emesis Onset	Time Post Dose
(b) (6)	T	(b) (6) @ 0834 hrs	(b) (6) @ 1600 hrs	7 hrs 26 min
	T	@ 0840 hrs	@ 1325 hrs	28 hrs 45 min
	R	@ 0840 hrs	@ 2255 hrs	14 hrs 15 min
	R	@ 0840 hrs	@ 1645 hrs	8 hrs 5 min

Although subject (b) (6) vomited within the dosing interval for period 2, this subject was included in the statistical analysis per the firm's protocol. Per DB policy, since the drug product is a transdermal patch (non-oral route of administration), vomiting will not influence drug absorption. The reviewer agrees with the firm's decision to include Subject (b) (6) in the statistical analysis. (For additional information, please see Appendix 4.7.1.)

The dropout subjects were not replaced. The protocol deviation did not affect the study outcome.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. R10-1307 Analyte Name: Rivastigmine								
Parameter	Standard Curve Samples							
Concentration (pg/mL)	100.0	200.0	500.0	1000	2000	4000	8000	10000
Inter day Precision (%CV)	1.2	1.7	3.4	1.8	1.8	1.5	2.0	2.8
Inter day Accuracy (%Bias)	-0.9	3.0	-1.8	-0.5	-3.7	-1.9	0.8	5.0
Linearity	"r ² " values: 0.997234 to 0.999709							
Linearity Range (pg/mL)	100.0 to 10000 pg/mL							
Sensitivity/LLOQ (pg/mL)	LLOQ 100.0 pg/mL							
Bioequivalence Study No. R10-1307 Analyte Name: Rivastigmine								
Parameter	Quality Control Samples							
Concentration (pg/mL)	LQC 300.0		MQC 3000	HQC 7500				
Inter day Precision (%CV)	5.4		4.4	3.3				
Inter day Accuracy (%Bias)	2.3		2.5	-1.4				

Comments on Study Assay Validation:

Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Acceptable.

Table 12. SOPs Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP (b) (4)	SOP Title
		Sample Analysis (Chromatographic)
		Sample Reanalysis and Reporting Criteria

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

The study assay is **adequate**.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in [Table 18](#) and [Figure 1](#)

Parameter	Unit	Test				Reference				Ratio (T/R)
		Mean	CV%	Min	Max	Mean	CV%	Min	Max	
AUCT	pg hr/mL	170290.4	28.64	95088.20	273540.3	151357.8	35.07	70189.70	300660.9	1.13
AUCI	pg hr/mL	171136.0	28.53	95979.30	273875.9	152261.1	34.91	71307.04	301554.0	1.12
C _{MAX}	pg/mL	9529.04	32.05	4767.00	14800.00	8355.33	39.52	3498.00	18560.00	1.14
T _{MAX}	Hr	10.00		8.00	24.00	10.00		4.00	26.00	1.00
KE	hr ⁻¹	0.29	17.98	0.20	0.44	0.27	11.56	0.21	0.33	1.04
THALF	Hr	2.50	17.28	1.59	3.54	2.56	11.81	2.10	3.23	0.98

* T_{max} values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Rivastigmine Transdermal System, 9.5 mg/24 hours Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. R10-1307				
Parameter (units)	Test	Reference	Ratio	90% C.I.
AUC _{0-t} (hr *pg/ml)	163464.95	143876.95	113.61	(106.60, 121.09)
AUC _∞ (hr *pg/ml)	164334.80	144824.77	113.47	(106.50, 120.90)
C _{max} (pg/ml)	9067.37	7869.17	115.23	(107.05, 124.02)

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Rivastigmine Transdermal System, 9.5 mg/24 hours Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. R10-1307					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (hr *pg/ml)	163479.0	143870.9	1.14	106.61	121.11
AUC _∞ (hr *pg/ml)	164348.9	144818.8	1.13	106.51	120.92
C _{max} (pg/ml)	9067.37	7869.17	1.15	107.05	124.02

Table 17. Additional Study Information, Fasting Study No. R10-1307

Root mean square error, AUC _{0-t}	0.1371	
Root mean square error, AUC _∞	0.1363	
Root mean square error, C _{max}	0.1582	
	Test	Reference
Kel and AUC _∞ determined for how many subjects?	27	27
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as C _{max}	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC _{0-t} /AUC _∞				
Treatment	n	Mean	Minimum	Maximum
Test	27	0.99	0.98	1.00
Reference	27	0.99	0.98	1.00

Comments on Pharmacokinetic and Statistical Analysis:

1. The pharmacokinetic measures (AUC_t, AUC_i, C_{max}, T_{max}, KE and t_{1/2}) and confidence intervals of AUC_t, AUC_i, and C_{max} for rivastigmine as calculated by the reviewer were in agreement with the values reported by the firm.
2. The 90% confidence intervals for rivastigmine of ln-transformed AUC_t, AUC_i, and C_{max} ratios are within the acceptable limits of 80-125%.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

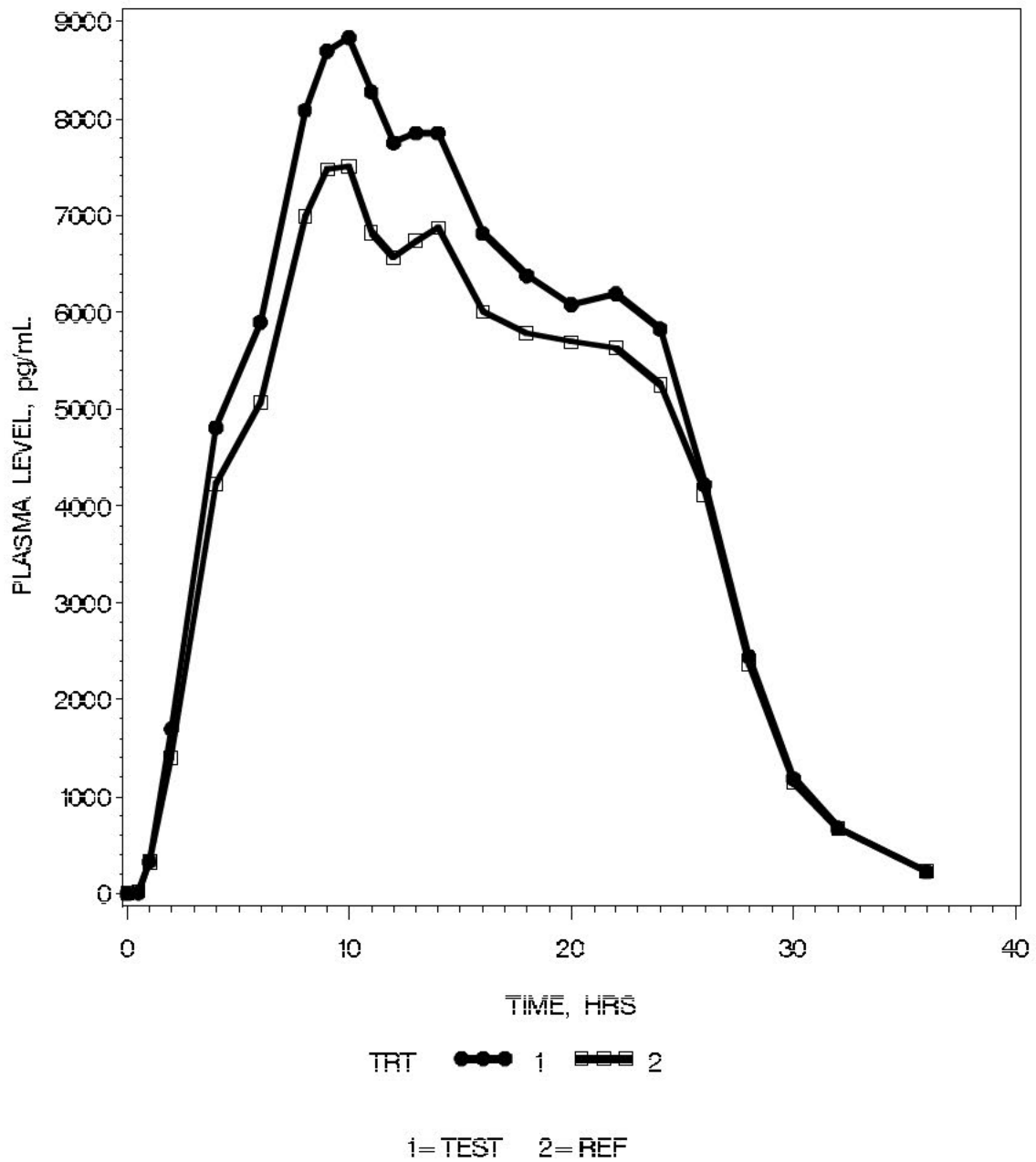
The fasting *in vivo* bioequivalence study is **adequate**.

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Time (hr)	Test (n=27)		Reference (n=27)		Ratio
	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.50	7.34	519.62	26.41	400.07	0.28
1.00	331.07	224.13	322.55	330.35	1.03
2.00	1700.86	103.16	1407.26	143.96	1.21
4.00	4810.49	54.35	4233.89	75.19	1.14
6.00	5898.81	46.83	5067.30	58.75	1.16
8.00	8084.41	41.47	6984.67	49.59	1.16
9.00	8698.59	36.25	7474.04	45.04	1.16
10.00	8836.93	35.02	7507.85	39.36	1.18
11.00	8277.78	35.19	6825.52	40.83	1.21
12.00	7750.26	34.63	6571.81	38.67	1.18
13.00	7849.93	31.93	6740.78	38.36	1.16
14.00	7851.30	28.67	6871.52	35.93	1.14
16.00	6815.07	30.21	6003.74	34.06	1.14
18.00	6378.74	28.78	5786.30	38.03	1.10
20.00	6081.63	28.02	5695.33	32.38	1.07
22.00	6191.37	30.54	5628.96	30.19	1.10
24.00	5827.67	29.35	5248.70	29.28	1.11
26.00	4220.52	32.90	4125.15	36.08	1.02
28.00	2449.34	39.81	2362.54	43.92	1.04
30.00	1184.47	57.33	1148.73	51.86	1.03
32.00	672.21	48.36	679.17	63.94	0.99
36.00	224.31	54.01	231.92	59.01	0.97

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

PLASMA RIVASTIGMINE LEVELS
RIVASTIGMINE TRANSDERMAL SYSTEM, 9.5 MG/24 HR, ANDA 204403
UNDER FASTING CONDITIONS
DOSE= 1 x 9.5 MG/24 HR



4.2 Formulation Data

Component	Function	Amount in dried matrix / %	Amount mg in 4.6 mg/24 hr Patch Size: 4.6 cm ²	Amount mg in: 9.5 mg/24 hr Patch Size: 9.2 cm ²	Amount mg in: 13.3 mg/24 hr Patch Size: 13.8 cm ²
Active layer, target area weight:					
Rivastigmine	API	25	6.9 mg	13.8 mg	20.7
(b) (4)					

From Module 3.2.P.1:

Rivastigmine transdermal system (Rivastigmine-TDS) is a matrix patch consisting of two matrix layers. It is available in three strengths, 4.6 mg/24 hr, 9.5 mg/24 hr and 13.3 mg/24 hr. The compositions of all strengths are the same and the only difference is the patch size. The patches are a circular shape.

An impermeable backing liner made from aluminum coated polyester combined with skin colored polyethylene has been chosen to protect the patch from the environment. The patch is situated on a standard release liner with fluoropolymer-coating. This liner is removed prior to application.

After manufacturing each transdermal patch, together with a cover sheet made of polyethylene terephthalate siliconized on one side, is individually packed into a heat-sealed sachet made of (b) (4)
(b) (4)

RIV-TDS is composed as shown in the following schematic drawing:

- a cover sheet: siliconized polyethylene terephthalate film
- a backing liner: Polyethylene / thermoplastic resin / aluminum coated polyester film
- an active reservoir layer containing the active pharmaceutical ingredient
- an adhesive matrix layer
- a release liner: fluoropolymer coated polyester film



Figure 1 Schematic drawing of newly developed Rivastigmine-TDS

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	See comments below.

Reviewer’s Comments:

1. The maximum daily dose for Rivastigmine Transdermal System is 13.3 mg/24 hours. Only one transdermal system of either the 4.6 mg/24 hour, 9.5 mg/24 hour or 13.3 mg/24 hours strengths are worn at any given time, according to the package insert for the RLD

(Exelon® Patch). Additionally, the patient package insert for the RLD (Exelon® Patch) states that every 24 hours the transdermal system should be removed and a new transdermal system should be applied.

2. The backing liner (b) (4) of the 13.3 mg/24 hour strength is proposed at a level of (b) (4), which exceeds the maximum level in the IIG Database. However, the liner should not be applied to the patients' skin as it is designed to protect the patch from the environment and discarded before the patch is placed on the skin. (This was also noted at the time of filing for the New Strength Amendment and was acceptable.²) Therefore, from a Bioequivalence perspective, the amount of backing liner used in this product is acceptable.
3. The inactive ingredients are within the acceptable IIG limits based on the MDD of 13.3 mg/24 hours.
4. The formulation is **adequate**.

² ANDA 204403 DARRTS REV-RPM-03(Filing Review); Submit Date: 5/20/2013

4.3 Dissolution Data

Dissolution Review Path	REV-BIOEQ-02(Dissolution Review) Submit Dates: 3/23/13, 5/17/13, 9/13/13, 9/24/13, and 12/19/13

Dissolution testing data are not reviewed in this review.

Per the “dissolution only” reviews, upon review of the dissolution data submitted in the original submission of June 12, 2012 and two dissolution amendments submitted on April 11, 2013 and May 2, 2013,^{3,4} the DB II found that the firm conducted acceptable regulatory dissolution testing using the following FDA-recommended dissolution method:

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

However, the firm’s proposed release specifications were found not acceptable. Based on the submitted data, in the deficiency letter dated May 23, 2013,⁵ the DB II recommended that the firm acknowledge the following release specifications for all strengths of the test product (4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr):

1 hr: (b) (4)
2 hr: (b) (4)
4 hr: (b) (4)
9 hr: (b) (4)
24 hr: (b) (4)

Since this is a modified release drug dosage form the firm has conducted multi media dissolution testing in pH 1.2 HCl Buffer, pH 4.5 Acetate Buffer, and pH 6.8 Phosphate Buffer on all strengths. Additionally the firm conducted dissolution testing on the 13.3 mg strength in pH (b) (4) Phosphate Buffer. However the firm did not submit dissolution summary tables for multimedia testing and did not specify rotation speed in any of the multimedia dissolution testing. In the amendment of April 11, 2013 the firm provided the rotation speed for multimedia dissolution testing, clarified that the detection method in dissolution method validation is UV, and provided the COA for all three strengths of the reference product. However, the firm did not submit dissolution summary tables for multimedia dissolution testing. In a bioequivalence telephone amendment request dated April 30, 2013, the DB II requested that the firm submit these summary tables. The firm submitted the dissolution summary tables for the multimedia dissolution testing in the amendment of May 2, 2013. The test products demonstrate no potential for dose-dumping in pH 1.2 HCl, pH 4.5 acetate, and pH 6.8 phosphate buffers.

³ ANDA 204403 – DARRTS: REV-BIOEQ-02(Dissolution Review) – 3/23/2013

⁴ ANDA 204403 – DARRTS: REV-BIOEQ-02(Dissolution Review) – 5/17/2013

⁵ ANDA 204403 – DARRTS: COR-ANDA-09(Bio Dissolution Deficiencies) – 5/23/2013

In its response dated June 20, 2013, the firm acknowledged the dissolution method mentioned above and accepted the DB II recommended release specifications at the 1 hour, 2 hour, and 9 hour time points. However, the firm proposed release specifications of (b) (4) % and NLT (b) (4) % at the 4 hour and 24 hour time points, respectively.

The DB II found the firm's proposed release specification of (b) (4) % at the 4 hour time point acceptable. However; the DB II found the specification of NLT (b) (4) % at the 24 hour time point not acceptable. The DB II acknowledged the firm's rationale that according to USP Chapter <1092> allowance needs to be made for assay and content uniformity ranges. However, USP Chapter <1092> also states that acceptance criteria including test times are usually established on the basis of an evaluation of the dissolution profile data. In the opinion of the DB II, a release specification of (b) (4) % at 24 hr adequately captures the terminal release profile of the test product and ensures better quality control against any possible overage in the future test product batches. The above mentioned DB recommended release specifications are based on the firm's submitted release data.

The firm was asked to provide adequate justification for its proposed release specification of NLT (b) (4) % at the 24-hour time point. Alternatively, the firm was asked to acknowledge the following DB II recommended dissolution method and revised DB II recommended release specifications:⁶

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications:
1 hr: (b) (4)
2 hr: (b) (4)
4 hr: (b) (4)
9 hr: (b) (4)
24 hr: (b) (4)⁷

In the November 11, 2013 submission, the firm accepted the Agency's proposed specifications for the 1 hr, 2 hr, 4 hr, and 9 hr time points. However, the firm requested that no upper limit be specified at the 24 hour time point, and proposed a dissolution specification of NLT (b) (4) % at the 24 hour time point.

The firm's rationale for eliminating the upper limit of (b) (4) % in the DB II recommended dissolution specification at the 24 hour time point (b) (4) % is that a batch with an assay value close to the upper limit of the (b) (4) % assay acceptance range will have more than (b) (4) % release at the 24 hour time point. In support of its rationale, the firm submitted summary

⁶ ANDA 204403 – DARRTS: REV-BIOEQ-02(Dissolution Review) – 9/24/2013

⁷ The 24 hour specification was amended to (b) (4) % from (b) (4) % on 9/24/2013

dissolution data on a new experimental batch of the 9.5 mg/24 hours strength (lot # P0022AK_319RIUTDS) with assay value of (b) (4) % showing average percent release of (b) (4) % (range (b) (4) %) at 24 hours. The firm also submitted summary dissolution data on another new experimental batch of the 9.5 mg/24 hours strength (lot # P0022AK_320RIUTDS) with assay value of (b) (4) % showing average percent release of (b) (4) % (range (b) (4) %) at 24 hours.

Per DB policy, dissolution specifications are set based on the data obtained on fresh bio lots and are not modified based on development, scale up or stability batch data. The above DB II recommended dissolution method and specifications were developed in consultation with the DB II Dissolution Focal Point⁸ based on the data submitted in the original application on the biostudy lot.

Specifying a range for percent dissolved at the 24 hour time point is consistent with *USP Chapter 24 – Table 1* recommendations for setting dissolution specifications for transdermal systems. Dissolution data from experimental batches that have assay values near or above the top end of assay acceptance range is not adequate justification for eliminating the upper limit for dissolution specification at the 24 hour time point. After consulting the DB II Dissolution Focal Point on acceptability of the firm's request to eliminate the upper limit at the 24 hour time point, the DB II management concluded that the upper limit at the 24 hour time point can not be eliminated. However, the DB II revised the upper limit at the 24 hour time point from (b) (4) % to (b) (4) %. The following revised dissolution specifications should be communicated to the firm:

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications:

1 hour: (b) (4)
2 hours (b) (4)
4 hours (b) (4)
9 hours (b) (4)
24 hours: (b) (4)

The firm was requested to acknowledge the above dissolution method and revised dissolution specifications.

The firm's dissolution testing is incomplete. The firm's response will be reviewed separately.

⁸ ANDA 204403 – DARRTS: REV-BIOEQ-02(Dissolution Review) – 12/19/2013

Dissolution Conditions		Apparatus:	Modified USP Type VI (Rotating Cylinder)										
		Medium:	0.9% NaCl at 32°C										
		Volume:	500 mL										
		Temperature:	32 ± 0.5°C										
		Rotation Speed	50 RPM										
Firm's Proposed Specifications:		Level 1: 6 patches are tested and each patch complies with the specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4) Level 2: 6 additional patches are tested and the mean of 12 patches (Level 1 + Level 2) must comply with the Level 1 specification above and no patch is allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4) Level 3: 12 additional patches are tested and the mean of 24 patches (Level 1 + Level 2 + Level 3) must comply with the above mentioned Level 1 specification. Maximum of two patches are allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4) and no patch is allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4)											
Dissolution Testing Site (Name, Address)		(b) (4)											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (hours)								Study Report Location
					0	1	2	4	7	9	12	24	

C10-1870	07/22/2011 – 8/8/2011	Rivastigmine Transdermal System / Batch No. C0002AL0AT (Manufactured – 06/27/2011)	4.6 mg/24 hr	12	Mean	0	23.53	38.01	57.69	73.72	79.59	84.64	90.60	Module 1.12.12
					Range	(b) (4)								
					%CV	-	3.09	1.72	1.68	1.82	2.07	2.03	1.58	
		Exelon Patch (Batch No. 1200 BA) Expiration Date: Oct 2012	4.6 mg/24 hr	12	Mean	0	40.10	56.34	69.83	78.10	81.04	84.06	89.64	Module 1.12.12
					Range	(b) (4)								
					%CV	-	0.69	0.80	0.86	0.90	0.92	0.98	1.05	
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes or hours)								Study Report Location	
					0	1	2	4	7	9	12	24		
C10-1870	07/18/2011 – 8/12/2011	Rivastigmine Transdermal System / Batch No. C0004AL0AU (Manufactured – 06/27/2011)	9.5 mg/24 hr	12	Mean	0	23.04	37.85	58.20	74.89	81.04	86.43	92.41	Module 1.12.12
					Range	(b) (4)								
					%CV	-	1.98	1.33	1.24	1.77	2.05	2.24	2.78	
		Exelon Patch (Batch No. 1401B) Expiration Date: Jan 2013	9.5 mg/24 hr	12	Mean	0	40.67	56.41	68.42	75.56	78.44	81.53	87.23	Module 1.12.12
					Range	(b) (4)								
					%CV	-	1.00	0.75	0.69	0.59	0.58	0.53	0.73	
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes or hours)								Study Report Location	
					0	1	2	4	7	9	12	24		
	11/20/2012	Rivastigmine	13.3	12	Mean	0	22.29	37.79	59.74	77.86	84.41	90.02	95.84	Module

	Transdermal System / Batch No. C0014AL0BC (Manufactured – 10/08/2012)	mg/24 hr		(b) (4), 2.7.1								
				Range								
	Exelon Patch (Batch No. 2302A BA) Expiration Date: April 2014	13.3 mg/24 hr	12	Mean	0	39.75	56.10	68.46	75.33	78.07	81.09	87.04
Range				(b) (4)								
				%CV	-	1.30	0.94	0.66	1.04	1.38	1.73	1.65
				%CV	-	1.85	0.98	0.93	0.85	0.97	0.95	0.81

Dissolution Conditions	Apparatus:	(b) (4)
	Medium:	
	Volume:	
	Temperature:	
	Rotation Speed	



Dissolution Conditions	Apparatus:	Modified USP Type VI (Rotating Cylinder)
	Medium:	Hydrochloric acid buffer pH 1.2
	Volume:	500 mL
	Temperature:	32 ± 0.5°C
	Rotation Speed	50 RPM

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)								Study Report Location
						0	1	2	4	7	9	12	24	
C10-1870	07/22/2011 - 8/8/2011	Rivastigmine Transdermal System / Batch No. C0002AL0AT (Manufactured - 06/27/2011)	4.6 mg/24 hr	12	Mean	0	27.14	42.79	62.54	77.23	82.60	87.07	92.47	Module 2.7.1
					Range	(b) (4)								
					%CV	-	3.22	2.25	1.40	1.07	1.06	1.05	1.59	
		Exelon Patch (Batch No. 1200 BA) Expiration Date: Oct 2012	4.6 mg/24 hr	12	Mean	0	47.74	61.87	72.43	78.40	80.50	82.61	86.19	
					Range	(b) (4)								
					%CV	-	1.44	0.92	0.76	0.74	0.73	0.77	0.76	

Dissolution Conditions	Apparatus:	Modified USP Type VI (Rotating Cylinder)
	Medium:	Acetate Buffer pH 4.5
	Volume:	500 mL

Study Ref No.	Testing Date	(Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours)								Study Report Location
						0	1	2	4	7	9	12	24	
C10-1870	07/22/2011 - 8/8/2011	Rivastigmine Transdermal System / Batch No. C0002AL0AT (Manufactured - 06/27/2011)	4.6 mg/24 hr	12	Mean	0	24.99	40.09	60.14	75.38	80.54	84.96	90.72	Module 2.7.1
					Range	(b) (4)								
					%CV	-	3.64	2.43	1.28	0.80	0.74	0.96	1.56	
		Exelon Patch (Batch No. 1200 BA) Expiration Date: Oct 2012	4.6 mg/24 hr	12	Mean	0	43.83	56.83	67.03	72.98	85.21	77.56	83.01	
					Range	(b) (4)								
					%CV	-	1.28	1.31	1.12	1.18	1.31	1.27	1.24	

Dissolution Conditions	Apparatus:	Modified USP Type VI (Rotating Cylinder)
	Medium:	Phosphate Buffer pH 6.8
	Volume:	500 mL
	Temperature:	32 ± 0.5°C
	Rotation Speed	50 RPM

C10-1870	07/22/2011 – 8/8/2011	Rivastigmine Transdermal System / Batch No. C0002AL0AT (Manufactured – 06/27/2011)	4.6 mg/24 hr	12	Mean	0	23.53	38.16	57.87	73.71	79.61	84.49	90.92	Module 2.7.1
					Range	(b) (4)								
					%CV	-	4.42	3.35	2.16	1.71	1.61	1.72	1.93	
		Exelon Patch (Batch No. 1200 BA) Expiration Date: Oct 2012	4.6 mg/24 hr	12	Mean	0	46.52	60.52	71.05	77.11	79.62	81.89	86.56	
					Range	(b) (4)								
					%CV	-	1.20	0.84	0.82	1.04	1.09	1.07	1.25	

Dissolution Conditions	Apparatus:	Modified USP Type VI (Rotating Cylinder)
	Medium:	Hydrochloric Acid buffer pH 1.2
	Volume:	500 mL
	Temperature:	32 ± 0.5°C
	Rotation Speed	50 RPM

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)								Study Report Location
						0	1	2	4	7	9	12	24	
C10-1870	07/18/2011 – 8/12/2011	Rivastigmine Transdermal System / Batch No. C0004AL0AU (Manufactured – 06/27/2011)	9.5 mg/24 hr	12	Mean	0	27.46	43.56	64.78	80.01	85.60	90.22	95.73	Module 2.7.1
					Range	(b) (4)								
					%CV	-	4.74	4.52	3.89	3.67	3.68	3.53	3.69	

		Exelon Patch (Batch No. 1401B) Expiration Date: Jan 2013	9.5 mg/24 hr	12	Mean	0	47.96	62.50	73.20	79.52	87.57	83.63	87.33	
					Range	(b) (4)								
					%CV	-	0.55	0.46	0.50	1.05	0.70	1.00	1.05	

Dissolution Conditions	Apparatus:	Modified USP Type VI (Rotating Cylinder)
	Medium:	Acetate Buffer pH 4.5
	Volume:	500 mL
	Temperature:	32 ± 0.5°C
	Rotation Speed	50 RPM
Firm's		

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)								Study Report Location
						0	1	2	4	7	9	12	24	
C10-1870	07/18/2011 - 8/12/2011	Rivastigmine Transdermal System / Batch No. C0004AL0AU (Manufactured - 06/27/2011)	9.5 mg/24 hr	12	Mean	0	26.19	41.76	62.07	77.26	82.32	86.51	91.61	Module 2.7.1
					Range	(b) (4)								
					%CV	-	3.97	2.91	2.00	2.03	2.24	2.28	2.60	
		Exelon Patch (Batch No. 1401B) Expiration Date: Jan 2013	9.5 mg/24 hr	12	Mean	0	44.0	58.59	69.55	75.96	78.51	81.14	87.34	
					Range	(b) (4)								
					%CV	-	1.54	0.63	0.60	0.79	0.87	0.79	1.00	

Dissolution Conditions	Apparatus:	Modified USP Type VI (Rotating Cylinder)
	Medium:	Phosphate Buffer 6.8
	Volume:	500 mL
	Temperature:	32 ± 0.5°C
	Rotation Speed	50 RPM

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)								Study Report Location
						0	1	2	4	7	9	12	24	
C10-1870	07/18/2011 - 8/12/2011	Rivastigmine Transdermal System / Batch No. C0004AL0AU (Manufactured - 06/27/2011)	9.5 mg/24 hr	12	Mean	0	25.14	40.34	60.66	76.04	81.51	86.13	91.43	Module 2.7.1
					Range	(b) (4)								
					%CV	-	5.0	3.52	2.12	0.77	0.62	0.60	0.98	
		Exelon Patch (Batch No. 1401B) Expiration Date: Jan 2013	9.5 mg/24 hr	12	Mean	0	48.56	62.99	73.69	79.89	82.25	84.56	89.17	
					Range	(b) (4)								
					%CV	-	0.47	0.26	0.27	0.25	0.30	0.33	0.49	

Dissolution Conditions	Apparatus:	Modified USP Type VI (Rotating Cylinder)
	Medium:	Hydrochloric Acid buffer pH 1.2
	Volume:	500 mL
	Temperature:	32 ± 0.5°C

No.	Date (Reference – Expiration Date)	& Form	Units												Location
11/20/2012	Rivastigmine Transdermal System / Batch No. C0014AL0BC (Manufactured – 10/08/2012)	13.3 mg/24 hr	12	Mean	0	27.59	44.66	66.85	83.56	89.03	91.43	97.59	(b) (4)		Module 2.7.1
				Range	(b) (4)										
	%CV	-	2.84	2.55	1.98	1.35	1.36	1.02	1.18						
	Mean	0	48.37	43.10	73.40	79.31	81.36	83.42	87.19	(b) (4)					
	Exelon Patch (Batch No. 2302A BA) Expiration Date: April 2014	13.3 mg/24 hr	12	Range	(b) (4)										
				%CV	-	1.99	0.91	0.50	0.35	0.30	0.41	0.52			

Dissolution Conditions	Apparatus:	Modified USP Type VI (Rotating Cylinder)
	Medium:	Acetate Buffer pH 4.5
	Volume:	500 mL
	Temperature:	32 ± 0.5°C
	Rotation Speed	50 RPM

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)								Study Report Location
						0	1	2	4	7	9	12	24	
	11/20/2012	Rivastigmine Transdermal System /	13.3 mg/24 hr	12	Mean	0	25.02	42.25	65.37	82.04	87.27	90.22	94.04	Module 2.7.1

	Batch No. C0014AL0BC (Manufactured – 10/08/2012)			Range	(b) (4)									
				%CV	-	1.94	1.53	1.29	0.66	0.90	0.71	0.82		
	Exelon Patch (Batch No. 2302A BA) Expiration Date: April 2014	13.3 mg/24 hr	12	Mean	0	42.43	55.79	66.42	72.54	74.72	77.17	82.64	(b) (4)	
				Range	(b) (4)									
				%CV	-	0.71	0.46	0.34	0.46	0.48	0.49	0.48		

Dissolution Conditions	Apparatus:	Modified USP Type VI (Rotating Cylinder)
	Medium:	Phosphate Buffer pH 6.8
	Volume:	500 mL
	Temperature:	32 ± 0.5°C
	Rotation Speed	50 RPM
Firm's	Level 1:	

Study Ref No.	Testing Date	Product ID / Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)								Study Report Location
						0	1	2	4	7	9	12	24	
	11/20/2012	Rivastigmine Transdermal System / Batch No. C0014AL0BC (Manufactured – 10/08/2012)	13.3 mg/24 hr	12	Mean	0	25.22	41.56	63.79	80.84	86.67	91.27	95.58	Module 2.7.1
					Range	(b) (4)								
					%CV	-	2.67	1.73	1.29	1.04	1.15	1.17	1.48	
		Exelon Patch (Batch No. 2302A BA) Expiration Date: April	13.3 mg/24 hr	12	Mean	0	48.48	62.76	73.16	79.06	81.27	83.42	87.78	(b) (4)
					Range	(b) (4)								
		2014												
					%CV	-	1.00	0.70	0.44	0.40	0.37	0.38	0.49	

4.4 Detailed Regulatory History (If Applicable)

ANDAs:

(b) (4)					
ANDA-205622	RIVASTIGMINE	MYLAN TECHNOLOGIES INC	PATCH	CDER/OGD	Refuse to Receive
ANDA-204403	RIVASTIGMINE	ALVOGEN INC	PATCH	CDER/OGD	Pending
(b) (4)					

Controls:

0180	Rivastigmine Transdermal Patch	BE recommendations/requirements	(b) (4)
08-0189	Rivastigmine Transdermal System	Request for BE and dissolution recommendations	
08-0231	Rivastigmine Transdermal Patch	BE studies and guidance.	
08-0526	Rivastigmine Extended Release Transdermal Film	BE/dissolution method recommendations	
10-0037	Rivastigmine Transdermal System	Requesting Pre-ANDA meeting.	
10-0371	Rivastigmine transdermal safety issue	Request for TDS irritation and sensitization study	
10-0716	Rivastigmine patch	Requesting formulation guidance.	
10-0729	Rivastigmine patch guidance questions	Requesting guidance in the development of this product.	
10-0749	Levels of vitamin D in Rivastigmine transdermal patch	Request for proposed formulation guidance.	

11-0107	Rivastigmine patch	Questions regarding this product.	(b) (4)
12-0205	Rivastigmine patch	Requesting study guidance. Opinion on the acceptability of the conduct of this study entirely at the Montreal site.	
12-0937	Rivastigmine Extended Release Transdermal Film	BE Guidance/Recommendation Rivastigmine Extended Release Transdermal Film	
12-1102	Rivastigmine Transdermal System - labeling MRI warning statement	Inactive Ingredient Review Rivastigmine Transdermal System - labeling MRI warning statement - (b) (4) backing Initially assigned to label	

Protocols:

None.

4.5 Consult Reviews

N/A

4.6 SAS Output

4.6.1 Fasting Study Data

FASTING CONCENTRATION DATASET

Obs	sub	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
1	(b) (6)	RT	1	R	0	0.0	0.0	253.8	3408.0	4680.0	6968	7168	6655	5326	4888	5758	6137	6037	5308	5374
2		RT	2	T	0	0.0	0.0	1086.0	4163.0	5101.0	7557	8250	8187	8197	7206	6739	7322	7256	6662	6450
3		TR	1	T	0	0.0	0.0	156.0	2912.0	3560.0	4872	5959	4415	5585	4888	5507	5311	4350	3695	3055
4		TR	2	R	0	0.0	111.0	598.4	3140.0	4046.0	6390	6302	5960	4952	4698	4490	4956	3906	4215	3656
5		TR	1	T	0	0.0	0.0	337.7	2667.0	3144.0	4345	4312	4721	4587	4153	4652	4908	3915	4024	3980
6		TR	2	R	0	0.0	328.3	2661.0	5152.0	6083.0	7774	7800	7234	6876	6391	6187	6358	5290	5675	4471
7		RT	1	R	0	0.0	0.0	0.0	787.1	1817.0	3477	3151	4417	4185	4080	4774	6392	3519	3819	4366
8		RT	2	T	0	0.0	0.0	0.0	2321.0	3288.0	4168	4650	6352	5421	5975	7012	7261	5730	7005	7239
9		RT	1	R	0	190.9	1113.0	3979.0	8173.0	8965.0	11910	12910	12660	12620	11280	10580	9965	8886	7137	6211
10		RT	2	T	0	198.2	1984.0	5480.0	10980.0	10560.0	12770	13590	14110	14730	14280	13170	12990	10590	9858	8800
11		TR	1	T	0	0.0	150.6	2161.0	5650.0	5911.0	8856	9966	9221	8603	7365	7639	8330	7605	7133	7745
12		TR	2	R	0	0.0	146.8	1843.0	4811.0	5824.0	7542	7734	8031	6610	6744	7349	7074	6352	5498	7303
13		RT	1	R	0	0.0	0.0	0.0	2126.0	1885.0	3976	5176	6047	5208	4610	5264	5573	4846	4444	4975
14		RT	2	T	0	0.0	0.0	1276.0	4964.0	7262.0	11190	11220	10940	9806	8726	9055	8868	6322	5122	6746
15		RT	1	R	0	0.0	0.0	0.0	0.0	632.2	2175	2779	3071	3345	4076	4438	4847	4926	5705	5630
16		RT	2	T	0	0.0	0.0	0.0	135.2	1336.0	2862	3699	3685	3911	4593	5478	5657	4289	4886	5363
17		RT	1	R	0	0.0	232.1	2695.0	7598.0	8296.0	9686	10310	9393	7900	8085	7791	7958	7258	6567	6424
18		RT	2	T	0	0.0	473.3	3247.0	7084.0	7493.0	11110	10390	9105	7763	7258	7610	7846	6792	5963	5803
19		TR	1	T	0	0.0	1614.0	4817.0	8754.0	12150.0	12770	12750	13240	11810	10620	9920	9256	8074	6907	6907
20		TR	2	R	0	0.0	342.0	2001.0	4081.0	6386.0	10390	10390	10260	9092	8017	7575	7960	7439	7093	6869
21		TR	1	T	0	0.0	3085.0	6901.0	10720.0	11660.0	14800	13460	11110	9233	8421	8221	7619	6077	5519	4442
22		TR	2	R	0	522.1	5510.0	8692.0	14560.0	12270.0	13440	12390	9749	7768	9143	8466	8730	5132	6039	5577
23		RT	1	R	0	0.0	0.0	763.0	2610.0	3107.0	4175	4843	4914	4295	3764	4048	4562	4353	3987	3897
24		RT	2	T	0	0.0	461.3	3435.0	4315.0	6163.0	7080	7514	7234	7585	6205	5761	5986	6064	4829	4661
25		RT	1	R	0	0.0	0.0	134.3	2906.0	3500.0	6106	6221	7410	6343	6346	6341	6917	6015	4977	5682
26		RT	2	T	0	0.0	0.0	1412.0	6231.0	8300.0	10620	12150	12910	10580	9553	9821	10450	10310	9000	8883

Obs	sub	seq	per	treat	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15	c16
27	(b) (6)	TR	1	T	0	0.0	0.0	1314.0	3307.0	7015.0	8257	11210	11100	10680	10250	10600	9837	7734	8675	8874
28		TR	2	R	0	0.0	178.8	1216.0	4711.0	5834.0	8781	9391	12700	11990	9947	12920	13310	9791	13790	11620
29		TR	1	T	0	0.0	0.0	1393.0	5399.0	7426.0	9462	10410	10980	11220	10710	10700	11030	10640	9891	7977
30		TR	2	R	0	0.0	0.0	488.7	3552.0	4694.0	6019	7029	7099	7033	6798	7531	7591	7504	6356	6512
31		TR	1	T	0	0.0	0.0	763.0	4420.0	4666.0	6439	7898	7264	8432	7761	6822	6956	6778	7839	6967
32		TR	2	R	0	0.0	0.0	742.8	4351.0	4589.0	5488	7287	7286	6875	6486	6546	6922	6188	6605	7001
33		RT	1	R	0	0.0	0.0	141.8	1684.0	3533.0	5636	6583	6172	5115	4808	5742	6672	5858	5099	5190
34		RT	2	T	0	0.0	0.0	190.4	1653.0	2060.0	3728	5014	6377	6404	5799	6071	5752	4548	4638	5212
35		RT	1	R	0	0.0	0.0	402.5	2530.0	3204.0	5070	5513	7694	7630	8567	7304	6377	8279	6534	6972
36		RT	2	T	0	0.0	0.0	569.9	4645.0	4355.0	7096	8964	12370	11910	12040	13050	11710	8180	7289	7345
37		RT	1	R	0	0.0	0.0	0.0	945.9	1453.0	2202	3234	3389	3333	3401	3498	3386	3299	3163	2506
38		RT	2	T	0	0.0	0.0	0.0	1492.0	2902.0	3886	3881	4343	3863	4159	4492	4767	4648	3960	3435
39		TR	1	T	0	0.0	0.0	2688.0	8570.0	8702.0	14630	14400	14060	13190	11930	11530	10590	9166	7845	6129
40		TR	2	R	0	0.0	604.1	6186.0	11680.0	13190.0	17860	18560	16420	14850	13850	14330	13700	11650	8985	8254
41		TR	1	T	0	0.0	0.0	1126.0	4634.0	5898.0	9655	9731	9394	8224	8228	8615	8345	7369	5975	5109
42		TR	2	R	0	0.0	0.0	453.7	3524.0	3804.0	6404	8020	7385	6897	5323	5070	5533	5247	4338	5026
43		TR	1	T	0	0.0	833.8	2572.0	5094.0	4922.0	7188	7330	6764	5742	5124	5069	5744	3438	3633	2930
44		TR	2	R	0	0.0	142.8	1184.0	4140.0	4376.0	5029	5315	4922	4284	4435	4537	3750	3479	3097	2864
45		RT	1	R	0	0.0	0.0	330.5	2420.0	2840.0	4352	4442	4562	3429	2898	3301	3090	2681	1959	3158
46		RT	2	T	0	0.0	214.8	900.0	2993.0	2718.0	4235	4761	5413	3683	3718	4248	4530	4382	3935	4381
47		TR	1	T	0	0.0	0.0	880.5	4797.0	6284.0	8165	9188	9191	8289	7683	7817	7230	7139	6687	6125
48		TR	2	R	0	0.0	0.0	1272.0	5689.0	7125.0	8507	8980	8425	8241	7821	7723	7114	6482	6102	6073
49		RT	1	R	0	0.0	0.0	801.5	2975.0	4104.0	5746	6526	7246	6905	7594	6801	6416	5450	6937	6698
50		RT	2	T	0	0.0	122.0	1345.0	3245.0	4304.0	5928	6688	7107	6551	6385	6101	6373	5726	6481	6388
51		RT	1	R	0	0.0	0.0	0.0	2163.0	3944.0	5237	6249	6965	6445	6308	6620	7162	6231	6380	6056
52		RT	2	T	0	0.0	0.0	1428.0	4673.0	6007.0	7503	7991	7974	7471	7296	7324	8148	7724	7567	6675
53		TR	1	T	0	0.0	0.0	444.6	4065.0	6081.0	9107	9486	11030	10030	8931	8924	9169	9161	7208	6583
54		TR	2	R	0	0.0	0.0	1156.0	4598.0	6636.0	8246	7496	6646	6742	7081	7017	7079	6003	6421	5409

Obs	c17	c18	c19	c20	c21	c22	c23
1	5468	5633	3349	2370.0	1054.0	571.6	179.2
2	6814	6229	4121	2514.0	1085.0	580.2	186.6
3	2721	3129	2233	1434.0	1127.0	816.3	167.4
4	4174	3993	2602	1469.0	760.3	627.2	179.7
5	4325	4182	2822	1458.0	610.3	408.2	188.3
6	4292	3782	2676	1444.0	498.4	291.7	114.5
7	4920	3849	3484	2981.0	1588.0	952.0	341.4
8	7140	7154	5020	3280.0	1771.0	1062.0	366.0
9	6462	6174	5999	2909.0	1148.0	578.4	174.6
10	7891	7773	6024	3113.0	1150.0	496.0	123.6
11	7247	6455	4209	2272.0	876.6	525.8	179.3
12	5824	4898	3595	2382.0	1233.0	518.3	204.5
13	6224	5541	6471	3877.0	1547.0	894.3	286.6
14	9479	7483	5482	2382.0	1317.0	665.8	180.1
15	6339	6683	4596	3191.0	1906.0	1288.0	529.2
16	6426	6907	5443	3338.0	1465.0	833.6	411.3
17	6341	5679	3755	2208.0	867.5	425.9	165.2
18	5600	4886	3321	1355.0	591.1	369.6	113.2
19	6449	5107	3221	2314.0	1007.0	580.7	185.2
20	6406	5889	4325	2169.0	1243.0	681.3	216.1
21	4254	3764	2286	1266.0	532.5	283.8	101.4
22	4875	4141	1971	1284.0	649.2	344.5	115.7
23	3838	3673	2798	1790.0	977.1	496.1	202.4
24	4654	4361	3455	1937.0	926.1	481.9	125.0
25	6765	6435	5015	2745.0	1279.0	820.8	316.3
26	8991	8655	6906	4211.0	1924.0	1048.0	501.4
27	9175	6931	6231	5171.0	3869.0	1680.0	537.9
28	10280	8449	8413	6130.0	3524.0	2511.0	740.0
29	9187	8062	6496	3729.0	1804.0	908.4	299.3
30	7529	7912	5336	2603.0	1108.0	566.9	185.0
31	7864	7780	5523	3191.0	1502.0	924.0	333.6
32	6530	5903	4793	2617.0	1041.0	629.4	247.5
33	4541	5060	4763	1967.0	1115.0	751.8	215.4
34	4773	7179	4713	2312.0	961.9	1200.0	197.6
35	6286	5392	5016	2181.0	1260.0	670.0	187.4
36	7772	8507	4756	3011.0	1442.0	693.4	178.7
37	2737	2202	2607	1484.0	823.7	668.3	253.3
38	3514	3681	2982	2096.0	917.9	561.5	215.2
39	5466	4936	4955	2484.0	1665.0	874.6	332.7
40	8832	7593	5860	3367.0	1631.0	982.2	274.1

Obs	c17	c18	c19	c20	c21	c22	c23
41	5951	5367	4372	2077.0	869.0	483.7	184.7
42	4391	5994	3989	1877.0	735.0	407.6	152.3
43	3257	2871	1942	814.1	275.4	152.7	0.0
44	2909	2708	2344	762.6	341.4	203.8	0.0
45	3121	2896	2069	1145.0	578.0	340.9	180.9
46	4447	3775	2254	1297.0	649.0	326.8	175.8
47	6181	5431	3325	1718.0	764.1	429.2	159.6
48	6182	5731	3285	1780.0	942.7	517.2	182.7
49	5844	4774	4263	2593.0	1266.0	504.6	194.2
50	5777	5459	3858	2548.0	1115.0	693.5	189.2
51	6128	6115	4390	2246.0	1088.0	609.8	240.4
52	6907	6709	4355	2517.0	883.4	550.5	224.6
53	4905	4574	3649	2293.0	880.4	519.4	198.6
54	4744	4616	3615	2217.0	811.5	484.0	183.3

FASTING PHARMACOKINETIC DATASET

Obs	sub	seq	per	treat	AUCT	AUCI	CMAX	TMAX	KE	THALF
1	(b) (6)	RT	1	R	137246.80	137855.19	7168	9.00	0.2945	2.35
2		RT	2	T	165430.30	166069.35	8250	9.00	0.2920	2.37
3		TR	1	T	101078.20	101587.01	5959	9.00	0.3290	2.11
4		TR	2	R	110586.04	111286.20	6390	8.00	0.2567	2.70
5		TR	1	T	100666.85	101629.43	4908	14.00	0.1956	3.54
6		TR	2	R	139754.63	140224.82	7800	9.00	0.2435	2.85
7		RT	1	R	101209.50	102541.94	6392	14.00	0.2562	2.71
8		RT	2	T	150353.32	151743.46	7261	14.07	0.2633	2.63
9		RT	1	R	225973.60	226533.54	12910	9.00	0.3118	2.22
10		RT	2	T	273540.30	273875.93	14730	11.00	0.3683	1.88
11		TR	1	T	184070.65	184746.91	9966	9.00	0.2651	2.61
12		TR	2	R	158757.50	159440.07	8031	10.00	0.2996	2.31
13		RT	1	R	127756.60	128774.73	6471	26.00	0.2815	2.46
14		RT	2	T	197223.60	197767.83	11220	9.00	0.3309	2.09
15		RT	1	R	112380.80	114844.22	6683	24.00	0.2148	3.23
16		RT	2	T	116644.30	118634.15	6907	24.00	0.2067	3.35
17		RT	1	R	185756.68	186286.45	10310	9.00	0.3118	2.22
18		RT	2	T	174896.88	175303.52	11110	8.00	0.2784	2.49
19		TR	1	T	223707.50	224362.58	13240	10.00	0.2827	2.45
20		TR	2	R	182398.54	183145.76	10390	8.00	0.2892	2.40
21		TR	1	T	198833.95	199204.45	14800	8.00	0.2737	2.53
22		TR	2	R	212463.85	212869.30	14560	4.00	0.2854	2.43
23		RT	1	R	100067.30	100816.98	4914	10.00	0.2700	2.57

Obs	sub	seq	per	treat	AUCT	AUCI	CMAX	TMAX	KE	THALF
24	(b) (6)	RT	2	T	143822.38	144196.30	7585	11.00	0.3343	2.07
25		RT	1	R	146129.95	147483.69	7410	10.00	0.2336	2.97
26		RT	2	T	239705.80	241663.08	12910	10.00	0.2562	2.71
27		TR	1	T	223031.80	224699.49	11210	9.00	0.3225	2.15
28		TR	2	R	266139.60	268976.34	13790	18.00	0.2609	2.66
29		TR	1	T	231393.30	232349.15	11220	11.00	0.3131	2.21
30		TR	2	R	164920.75	165546.38	7912	24.00	0.2957	2.34
31		TR	1	T	175869.05	177196.39	8432	11.00	0.2513	2.76
32		TR	2	R	155925.19	156962.70	7287	9.00	0.2386	2.91
33		RT	1	R	127382.14	128168.90	6672	14.00	0.2738	2.53
34		RT	2	T	124265.60	124930.02	7179	24.00	0.2974	2.33
35		RT	1	R	152175.05	152764.85	8567	12.00	0.3177	2.18
36		RT	2	T	204402.36	204917.75	13050	13.00	0.3467	2.00
37		RT	1	R	70189.70	71307.05	3498	13.00	0.2267	3.06
38		RT	2	T	95088.20	95979.41	4767	14.00	0.2415	2.87
39		TR	1	T	230097.20	231343.25	14630	8.00	0.2670	2.60
40		TR	2	R	300660.88	301554.13	18560	9.00	0.3069	2.26
41		TR	1	T	169871.92	170594.50	9731	9.00	0.2556	2.71
42		TR	2	R	130658.45	131244.18	8020	9.00	0.2600	2.67
43		TR	1	T	112348.96	112699.48	7330	9.00	0.4356	1.59
44		TR	2	R	92788.97	93406.74	5315	9.00	0.3299	2.10
45		RT	1	R	77409.25	78146.25	4562	10.00	0.2455	2.82
46		RT	2	T	99475.60	100131.90	5413	10.00	0.2679	2.59
47		TR	1	T	165090.25	165706.35	9191	10.00	0.2590	2.68
48		TR	2	R	167229.90	167857.39	8980	9.00	0.2912	2.38
49		RT	1	R	146227.45	146831.49	7594	12.00	0.3215	2.16
50		RT	2	T	145653.40	146270.91	7107	10.00	0.3064	2.26
51		RT	1	R	142977.70	143943.44	7162	14.00	0.2489	2.78
52		RT	2	T	173810.00	174796.58	8148	14.00	0.2277	3.04
53		TR	1	T	177110.05	177913.90	11030	10.00	0.2471	2.81
54		TR	2	R	151663.10	152404.56	8246	8.00	0.2472	2.80

4.6.2 Fasting Study Codes

```

/*-----
-----
/ Program   : BE02dp7.SAS (Updated: 27 March 2007)
/ SubMacros : macrolib.sas, continu2.sas, continu.sas, calcke.sas
/ Purpose   : To analyze two-way crossover bioequivalence studies.
/ Notes     :
/

```

```

/=====
=====
/ PARAMETERS:
/-----name----- -----description-----
-----

/=====
=====
/ AMENDMENT HISTORY:
/ Init --Date-- -----Description-----
-----
/
/=====
=====*/
**** NODATE OPTION generates error in word document.. with bodytitle
ods ****;

*****FOLLOW THE STEPS 1-16 TO RUN THIS PROGRAM*****;

OPTIONS PS=80;

***** LOCATION OF MACRO FILE (MACROLIB.SAS). CHANGE LOCATION IF
APPLICABLE *****;
%INCLUDE "C:\Documents and Settings\MILLERJEN\Desktop\SAS
Programs\Macros old\MACROLIB.SAS";

/*****
ASSIGN WHETHER HAVE GROUP EFFECT:
TRTGROUP = 1 TRT*GROUP INTERACTION IN GLM MODEL
TRTGROUP = 2 TRT*GROUP INTERACTION NOT IN GLM MODEL
TRTGROUP = NO GROUP EFFECT IN STUDY
NOTE: group variable has to be named GRP in the dataset.
*****/;

*****STEP 1: ASSIGN FLAG FROM ABOVE FOR TREAT*GROUP INTERACTION*****;
%let trtgroup=;

*****STEP 2: ENTER ANDA INFORMATION *****;
%let level = RIVASTIGMINE;
%let drug= RIVASTIGMINE TRANSDERMAL SYSTEM, 9.5 MG/24 HR;
%let dose= 1 x 9.5 MG/24 HR;
%let anda=204403;
%let studytype=FASTING;

***** STEP 3: ENTER LOCATION OF DATASETS AND LOCATION FOR SAVING OUTPUT
REPORTS *****;
%let studydir=C:\Documents and Settings\MILLERJEN\Desktop\SAS
Files\204403;

*****STEP 4: ENTER UNITS FOR PK PARAMETERS *****;
%let aucunit = pg hr/mL;
%let cmaxunit = pg/mL;
%let timeunit = hr;

***** STEP 5: SPECIFY NAME OF THE CONCENTRATION SAS DATASET *****;
***** IGNORE THIS STEP IF DATA IS FROM EXCEL *****;
%let cdata=plasma;

```

```

*****STEP 6: SPECIFY NAME OF THE PK SAS DATASET *****;
***** IGNORE THIS STEP IF DATA IS FROM EXCEL *****;
%let pdata=pk;

**** DO NOT CHANGE: NAME OF MS WORD STATISTICAL OUTPUT FILE ****;
%LET ODSFILE=&studydir\&anda._&studytype._stat_&level.CONTINU2.doc;

**** DO NOT CHANGE: NAME OF MS WORD REVIEW TABLES OUTPUT FILE ****;
%LET ODSFILE1=&studydir\&anda._&studytype._table_&level.CONTINU2.doc;

**** DO NOT CHANGE: NAME OF PLASMA CONCENTRATION PLOT IN CGM GRAPHIC
FILE****;
%LET PLOTFILE=&studydir\&anda._&studytype._plot_&level..cgm;

**** DO NOT CHANGE: NAME OF CONC AND PK DATASETS OUTPUT ****;
%LET
CONCOUTPUT=&studydir\&anda._&studytype._Datasets_&level.CONTINU2.doc;

%LET VARSORT=SUB PER;

%GLOBAL SUB PER SEQ TRT TREAT C T AUCT CMAX TMAX AUCI KE DF NNAME
THALF CLAST KE_FIRST KE_LAST OLDNAME NEWNAME;

*****STEP 7: SELECT TYPE OF ANALYSIS FROM BOTTOM*****;

/****SELECT CALCKE.SAS IF YOU WANT TO CALCULATE KE AND OTHER PARAMETERS
*** /
/****SELECT CONTINU.SAS IF YOU DO NOT WANT TO RECALCULATE KE. SPONSOR'S
KE WILL BE
USED FOR CALCULATION OF OTHER PARAMETERS WITH STATISTICS ON SPONSOR
SUPPLIED
PARAMETERS. FOR STATISTICS ON CALCULATED PARAMETERS USE CONTINU2.SAS
*** /

%LET FNAME=%QUOTE(M:\SAS\SASd\BEPRG\CONTINU.SAS);
%LET FNAME=%QUOTE(C:\Documents and Settings\MILLERJEN\Desktop\SAS
Programs\Macros old\CONTINU2.SAS);
*LET FNAME=%QUOTE(M:\SAS\SASd\BEPRG\CALCKE.SAS);
/**** WRITE DATA FILE NAMES *** /

*****STEP 8: BLOOD LEVEL DATA: NEED FILE NAME, FIRST OBSERVATION AND
VARIABLE LIST *****;

/**** IF NO BLOOD DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 3 *** /
/**** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE
THE NEXT LINE */
*FILENAME ORGPLASM DDE 'EXCEL|conc!R2C1:R73C26';
* FILENAME ORGPLASM "&studydir.\&plasmadata";
%LET FIRSTOBS=1; /* FIRST OBSERVATION */
%LET VARPLASM=SUB SEQ PER TRT c1-c22; /* VARIABLE LIST FOR THE
PLASMA DATA FILE */
%LET PLASMLS=900; /* INCREASE LINE SIZE IF NEEDED */
%READDATA (ORGPLASM, PLASMA, &FIRSTOBS, &VARPLASM, &PLASMLS)

```

```

*RUN;

*** IF EXCEL FILE, ACTIVATE THESE STATEMENTS ***;
FILENAME ORGPLASM DDE 'EXCEL|plasma!R2C1:R55C27';
%LET FIRSTOBS=1; /* FIRST OBSERVATION */

** IF INPUT FILE IS A SAS DATASET **;
** SPECIFIY LIBNAME WHERE THE SAS DATASET IS SAVED **;
*LIBNAME libdata "&studydir";

DATA PLASMA;

** IF USING EXCEL FILE ACTIVATE THESE STATEMENTS **;
infile ORGPLASM;
input sub seq $ per treat $ c1-c23;

/** IF SAS DATASET, ACTIVATE THESE STATEMENTS **;

SET LIBDATA.&CDATA;

RENAME SUBJECT = SUB SEQUENCE=SEQ PERIOD=PER;
IF PRODUCT = "B:REFERENCE FED" THEN TRT=2;
ELSE TRT=1;

RUN;

%SORTDS (PLASMA, &VARSORT)
RUN;

*****STEP 9:PK PARAMETER DATA: NEED FILE NAME, FIRST OBSERVATION AND
VARIABLE LIST *****;

/**IF NO PK PARAMETER DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4
***/
/** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE
THE NEXT LINE */
*FILENAME ORGPARAM DDE 'EXCEL|pk!R2C1:R73C10';
* FILENAME ORGPARAM "&studydir.\&pkdata";
*%LET FIRSTOBS=1; /* FIST OBSERVATION */
*%LET VARPARAM=SUB SEQ PER TRT AUCT AUCI CMAX TMAX KE THALF; /*
VARIABLE LIST */
%LET PARAMLS=500; /* INCREASE LINE SIZE IF NEEDED */
*%READDATA (ORGPARAM, PARAME, &FIRSTOBS, &VARPARAM, &PARAMLS)
*RUN;

*** IF EXCEL FILE, ACTIVATE THESE STATEMENTS ***;
FILENAME ORGPARAM DDE 'EXCEL|PK!R2C1:R55C10';
%LET FIRSTOBS=1; /* FIRST OBSERVATION */

DATA PARAME;

** IF USING EXCEL FILE ACTIVATE THESE STATEMENTS **;

```

```

infile ORPARAM;
input sub seq $ per treat $ AUCT AUCI CMAX TMAX KE THALF;

/** IF SAS DATASET, ACTIVATE THESE STATEMENTS **;

SET libdata.&PDATA;

RENAME SUBJECT = SUB SEQUENCE=SEQ PERIOD=PER;
IF PRODUCT = "B:REFERENCE FED" THEN TRT=2;
ELSE TRT=1;

RENAME AUCTLQC=AUCT
      AUCINF=AUCI
      KELM=KE;

RUN;

%SORTDS (PARAME, &VARSORT)
RUN;

/****FILENAME OF THE MERGED DATA****/
/****IF NO MERGED DATA, BLOCK READDATA AND SORTDS AND GO TO STEP 4 ****/
/**** IF DATA ON EXCEL WORKSHEET ACTIVATE THE LINE WITH DDE AND CLOSE
THE NEXT LINE */
*FILENAME ORGMERGE DDE 'EXCEL|SHEET1!R2C1:R101C29';
* FILENAME ORGMERGE 'C:\Data\Firms\ivax\76634\Fasting\FDA.1';
*%LET FIRSTOBS=1;  /****WRITE LINE NUMBER FOR THE FIRST OBSERVATION****/
*%LET VARMERGE=SUB PER SEQ TREAT $ C1-C18 AUCT AUCI CMAX TMAX THALF KE
GRP;
*%LET MERGELS=300; /* INCREASE LINE SIZE IF NEEDED */
*%READDATA (ORGMERGE, MERGED, &FIRSTOBS, &VARMERGE, &MERGELS)
*RUN;
*%SORTDS (MERGED, &VARSORT)
*RUN;

*****STEP 10: ADD OR REDUCE THE BLOOD SAMPLE NUMBER TO FIT THE STUDY
*****;
%LET CONCENT=%STR (C1, C2, C3, C4, C5, C6, C7, C8, C9, C10,
                  C11, C12, C13, C14, C15, C16, C17, C18, C19,
                  C20, C21, C22, C23);

*****STEP 11: ADD OR REDUCE THE SAMPLING TIME POINTS AND CHANGE THE
TIME *****;
%LET TIME=%STR (T1=0; T2=0.5; T3=1; T4=2; T5=4;
                T6=6; T7=8; T8=9; T9=10; T10=11;
                T11=12; T12=13; T13=14; T14=16; T15=18;
                T16=20; T17=22; T18=24; T19=26; T20=28; T21=30;
                T22=32; T23=36);

*****STEP 12: WRITE THE TOTAL NUMBER OF SAMPLING TIME POINTS *****;
%LET NO_ASSAY=23;

```

```

*****STEP 13: INITIALIZE KE_FIRST AND KE_LAST FOR KE CALCULATION IF
THESE ARE NOT
IN THE DATA SUBMITTED. *****;
%LET KE_FIRST=&NO_ASSAY-4;
%LET KE_LAST=&NO_ASSAY-0;

*****STEP 14: SUBJECTS/RECORDS TO BE REMOVED FROM CALCULATION *****;
/****VARIOUS SCREENING CONDITIONS CAN BE APPLIED FOR SUBJECT REMOVAL****/
/****LEAVE AS IT IS IF NO CHANGE IS DESIRED****/
/* %LET REMOVSUB=%STR(IF SUB^=10;IF SUB^=15;IF SUB^=34;IF SUB^=37;IF
SUB^=49); */
*%LET REMOVSUB=%STR(IF SUB^=23);

*****STEP 15: IF SEQ, PER, TRT OR OTHER VARIABLES TO BE ADDED OR
MODIFIED *****;
/****CREATING NUMERIC VARIABLES FROM CHARACTER VARIABLES, ETC ****/
/**** IF KE_FIRST AND KE_LAST ARE SUBMITTED IN THE DATA SET , KEEP THEM
CLOSED ****/
%LET ADD_VAR=%STR(KE_FIRST=&KE_FIRST; KE_LAST=&KE_LAST;
IF TREAT='T' THEN TRT=1; ELSE TRT=2;
IF SEQ='TR' THEN SEQ=1; ELSE SEQ=2);

DATA ORIGIN;
    ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
    ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
SET PLASMA;
SET PARAME;
*SET MERGED;
&TIME;
KE_FIRST=0;
KE_LAST=0;
CLAST=C&NO_ASSAY;
NEWCMAX=MAX(&CONCENT);

/****DO NOT CHANGE: TITLES FOR TABLES****/
%LET TITLE1=MEAN PLASMA &level LEVELS;
%LET TITLE2=MEAN PLASMA &level LEVELS FOR TEST AND REFERENCE PRODUCTS;

/**** DESCRIBE TITLES, FOOTNOTES AND LABELS FOR GRAPH ****/
%LET TITLE3=PLASMA &level LEVELS;
%LET TITLE4= &drug, ANDA &anda;
%LET TITLE5=UNDER &STUDYTYPE CONDITIONS;
%LET TITLE6=DOSE= &dose;
%LET FOOTNOT1=1=TEST 2=REF;
%LET FOOTNOT2=Tmax values are presented as median, range.;
%LET FOOTNOT3=;
%LET FOOTNOT4=;
%LET FOOTNOT5=;
%LET LABEL1=PLASMA LEVEL, &cmaxunit;

```

```

%LET LABEL2=TIME, HRS;
%LET LABEL3=TEST;
%LET LABEL4=REFERENCE;

%COPYDS (ORIGIN, NEW)
RUN;

*****STEP 16: OPEN IF YOU WANT TO REMOVE, ADD OR EDIT*****;
%*REMUVSUB (NEW, NEW)
RUN;

*****DO NOT CHANGE ANY OF THE STATEMENTS BELOW THIS LINE
*****;
*****YOU CAN NOW SUBMIT/RUN THE
PROGRAM*****;

%ADVVARIA (NEW, NEW)
RUN;

%RITEDATA (NEW, NEW, SUB TRT KE_FIRST KE_LAST) /***** TO EDIT KE-FIRST
AND KE-LAST**/
RUN;

%COPYDS (NEW, NEWCONC)
RUN;

*** dataset for data _null_***;
data updatedconc;
  set new;
run;

DATA NEWCONC;
  ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
  ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
  NO_ASSAY=&NO_ASSAY;
SET NEWCONC;
/* TRANSVERSE THE C AND T DATA INTO COLUMNS WITH NEW VARIABLE
NAMES */
DO I=1 TO NO_ASSAY;
  TIME=T(I);
  CONC=C(I);
  I=I;
OUTPUT;
END;

proc template;
  define style mystyle;
    parent = styles.rtf;
    REPLACE fonts /
      'headingFont' = ("Arial", 8pt,Bold)

```

```

    'docFont' = ("Arial", 8pt)
'TitleFont2' = ("Arial", 8pt, Bold)
    'TitleFont' = ("Arial", 8pt, Bold)
    'StrongFont' = ("Arial", 8pt, Bold)
    'EmphasisFont' = ("Arial", 8pt)
    'FixedEmphasisFont' = ("Arial", 8pt)
    'FixedStrongFont' = ("Arial", 8pt, Bold)
    'FixedHeadingFont' = ("Arial", 8pt, Bold)
    'BatchFixedFont' = ("Arial", 8pt)
    'FixedFont' = ("Arial", 8pt)
    'headingEmphasisFont' = ("Arial", 8pt, Bold);

style SysTitleAndFooterContainer from Container /
outputwidth = 85%
cellpadding = 2
cellspacing = 2
borderwidth = 0;

REPLACE Body from Document /
    bottommargin = 1.0in
    topmargin = 1.0in
    rightmargin = 0.25in
    leftmargin = 0.25in;
END;
run;

proc template;
define style mystyle1;
parent = styles.rtf;
REPLACE fonts /
    'headingFont' = ("Arial", 8pt, Bold)
    'docFont' = ("Arial", 8pt)
'TitleFont2' = ("Arial", 8pt, Bold)
    'TitleFont' = ("Arial", 8pt, Bold)
    'StrongFont' = ("Arial", 8pt, Bold)
    'EmphasisFont' = ("Arial", 8pt)
    'FixedEmphasisFont' = ("Arial", 8pt)
    'FixedStrongFont' = ("Arial", 8pt, Bold)
    'FixedHeadingFont' = ("Arial", 8pt, Bold)
    'BatchFixedFont' = ("Arial", 8pt)
    'FixedFont' = ("Arial", 8pt)
    'headingEmphasisFont' = ("Arial", 8pt, Bold);

style SysTitleAndFooterContainer from Container /
outputwidth = 85%
cellpadding = 2
cellspacing = 2
borderwidth = 0;

REPLACE Body from Document /
    bottommargin = 1.0in
    topmargin = 1.0in
    rightmargin = 1in
    leftmargin = 1in;
END;
run;

```

```

options orientation=landscape papersize=letter;

ods rtf file="&concoutput" style=mystyle bodytitle;

TITLE "&STUDYTYPE CONCENTRATION DATASET";
proc print data=plasma;
run;

TITLE "&STUDYTYPE PHARMACOKINETIC DATASET";
proc print data=parame;
run;
ods rtf close;

/* DETERMINE NEWTMAX, KE_FIRST, KE_LAST, NEWAUCT AND AUCLST */
DATA NEW;
    ARRAY C(&NO_ASSAY) C1-C&NO_ASSAY;
    ARRAY T(&NO_ASSAY) T1-T&NO_ASSAY;
    NO_ASSAY=&NO_ASSAY;
SET NEW;
CLAST=C&NO_ASSAY;
NEWCMAX=MAX(&CONCENT);

/* CALCULATE THALF IF THALF IS NOT GIVEN */
/* THALF=LOG(2)/KE; */
/* DETERMINE NEWTMAX */
DO I=1 TO NO_ASSAY;
IF C(I)=NEWCMAX THEN NEWTMAX=T(I);
END;
/* INTERPOLATE MISSING VALUE ON LINEAR SCALE */
IF C(1)=. THEN C(1)=0; /* MISSING VALUE */
IF C(NO_ASSAY)=. THEN C(NO_ASSAY)=0; /* MISSING VALUE */
DO I=2 TO (NO_ASSAY-1);
    H=I-1;
    J=I+1;
IF C(I)=. THEN DO; /* FIRST MISSING VALUE */
IF C(J)=. THEN J=J+1; /* SECOND CONSECUTIVE MISSING VALUE */
IF C(J)=. THEN J=J+1; /* THIRD CONSECUTIVE MISSING VALUE */
C(I)=C(H)+((C(J)-C(H))/(T(J)-T(H)))*(T(I)-T(H));
    END;
    END;
NEWTMAX=NEWTMAX;
/* CALCULATE AUCLST(TO THE LAST SAMPLING TIME POINT) */
AUCLST=0;
DO I=2 TO NO_ASSAY;
K=I-1;
AUCLST=AUCLST+((C(K)+C(I))*(T(I)-T(K))/2);
END;

/* CALCULATE AUCT AND STORE AS NEWAUCT(TO THE LAST DETECTABLE
CONC) */

```

```

DO I=NO_ASSAY TO 2 BY -1;
IF C(NO_ASSAY)>0 THEN DO;
    NEWAUCT=AUCLST;
    CLAST=C(NO_ASSAY);
    GOTO F;
END;
ELSE DO;
    K=I-1;
    IF C(I)=0 AND C(K)>0 THEN DO;
        NEWAUCT=AUCLST-(C(I)+C(K))*(T(I)-T(K))/2;
        CLAST=C(K);
        GOTO F;
    END;
END;
END;

F: NEWAUCT=NEWAUCT; /* FLAG TO CONTINUE */
NEWAUCI=NEWAUCT+CLAST/KE;
/* TRANSVERSE THE C AND T DATA INTO COLUMNS WITH NEW VARIABLE
NAMES */
DO I=1 TO NO_ASSAY;
TIME=T(I);
CONC=C(I);
IF CONC=0 OR CONC=. THEN LOGCONC=.;
ELSE LOGCONC=LOG(CONC);
NEWAUCT=NEWAUCT;
I=I;
OUTPUT;
END;
/* PROC PRINT;
RUN; */

data _null_;
    set updatedconc(where=(trt=1)) end=last;

    if last then call symput('testsub',trim(left(_N_)));
run;

data _null_;
    set updatedconc(where=(trt=2)) end=last;

    if last then call symput('refsub',trim(left(_N_)));
run;

/* PROC GLM CALCULATE LSMEANS */
%MACRO GRPANALYSIS (TRTGP=);

    /** TRTGRP INTERACTION **/
    %if &trtgp=1 %then
    %do;
        %PROCGLM(BASE,2,SUB TRT PER SEQ
GRP,AUCT,AUCI,CMAX,LAUCT,LAUCI,LCMAX,
, , , , , ,GRP SEQ SEQ*GRP SUB(SEQ*GRP) PER(GRP) TRT TRT*GRP,SEQ
GRP,SUB(SEQ*GRP))
        RUN;

```

```

%end;

/** No TRT*GRP Interaction **/
%else %if &trtgp=2 %then
%do;
%PROCGLM(BASE,2, SUB TRT PER SEQ
GRP, AUCT, AUCI, CMAX, LAUCT, LAUCI, LCMAX,
, , , , , , GRP SEQ SEQ*GRP SUB (SEQ*GRP) PER (GRP) TRT, SEQ
GRP, SUB (SEQ*GRP) )
RUN;
%end;

/** NO GROUP EFFECT **/
%else %do;
%PROCGLM(BASE,2, SUB TRT PER SEQ, AUCT, AUCI, CMAX, LAUCT, LAUCI, LCMAX,
, , , , , , SEQ SUB (SEQ) PER TRT, SEQ, SUB (SEQ) )
RUN;
%end;

%MEND GRPANALYSIS;

/* STATISTICS ON SUBMITTED DATA WITHOUT RECALCULATION */
DATA BASE;
SET NEW;
IF I=NO_ASSAY;

LAUCT=LOG (AUCT) ;
LAUCI=LOG (AUCI) ;
LCMAX=LOG (CMAX) ;
AUCRATIO=AUCT/AUCI;
OUTPUT;

/* TO RECALCULATE KE */
%INCLUDE "&FNAME";

/* PRINT SUMMARY OF PARAMETERS */
%LET TITLE=SUMMARY OF PARAMETERS;
%*PRINT(BASE, &TITLE)
RUN;

options orientation=portrait papersize=letter;

TITLE "&STUDYTYPE STATISTICAL OUTPUT";
ods rtf file="&odsfile" style=mystyle1 bodytitle;

ods rtf exclude LSMeans;
ods rtf exclude AUCT.OverallANOVA
AUCT.FitStatistics
AUCT.ModelANOVA
AUCT.AltErrTests
AUCT.Estimates
AUCI.OverallANOVA
AUCI.FitStatistics
AUCI.ModelANOVA

```

```

        AUCI.AltErrTests
        AUCI.Estimates
        CMAX.OverallANOVA
    CMAX.FitStatistics
        CMAX.ModelANOVA
        CMAX.AltErrTests
        CMAX.Estimates;

ods listing exclude LSMeans;

ods output "Fit Statistics"=fitstat;
%GRPANALYSIS (TRTGP=&TRTGROU);

DATA GLMOUT;
SET GLMOUT;
RENAME NAME_ =NNAME;
DATA LSMOUT;
SET LSMOUT;
RENAME _NAME_ =NNAME;
/* TRANSFER DF FROM GLMOUT TO LSMOUT3 FOR CI CALCULATIONS */
DATA GLMOUT1;
SET GLMOUT;
IF _SOURCE_='ERROR';
IF NNAME='AUCT' OR
   NNAME='AUCI' OR
   NNAME='CMAX';
/* KEEP NNAME _SOURCE_ DF; */
%SORTDS (GLMOUT1, NNAME)
RUN;
%*PRINT (GLMOUT1, GLMOUT1)
RUN;
%*LET TITLE=LSMEANS AND STANDARD ERRORS;
%*PRINT (LSMOUT, &TITLE)
RUN;

/* CALCULATE T AND 90% CI FOR NON-TRANSFORMED DATA */
%LSMFILE (LSMOUT, TRT, 2, AUCT, AUCI, CMAX, X, X, X, NNAME, OR)
RUN;

%MERGMULT (2, LSMOUT, GLMOUT1, , , LSMDAT, NNAME)
RUN;
DATA LSMDAT;
SET LSMDAT;
/* FOR 90% CI, P=0.95 */

/* CALCULATION OF T BASED ON P AND DF */
%CI (0.95, 2);
%*PRINT (LSMDAT, LSMDAT)
RUN;

%LET TITLE=90% CONFIDENCE INTERVALS ON NON-TRANSFORMED DATA;
%*PRINT (LSMDAT, &TITLE)
RUN;

/* TRANSFER DF FROM GLMOUT TO LSMOUT33 FOR CI CALCULATIONS */

```

```

DATA GLMOUT11;
SET GLMOUT;
IF _SOURCE_='ERROR';
IF NNAME='LAUCT' OR
   NNAME='LAUCI' OR
   NNAME='LCMAX';
/* KEEP NNAME _SOURCE_ DF; */
%SORTDS(GLMOUT11, NNAME)
RUN;

/* CALCULATE T AND 90% CI FOR LOG-TRANSFORMED DATA */
%LSMFILE(LSMOUT, TRT, 2, LAUCT, LAUCI, LCMAX, , , NNAME, OR)
RUN;

%MERMULT(2, LSMOUT, GLMOUT11, , , LLSMDAT, NNAME)
RUN;
DATA LLSMDAT;
SET LLSMDAT;
/* FOR 90% CI, P=0.95 */
%CILOG(0.95, 2);

%LET TITLE=90% CONFIDENCE INTERVALS ON LOG-TRANSFORMED DATA;
%*PRINT(LLSMDAT, &TITLE)
RUN;

/* STATISTICS ON TRT1/TRT2 RATIO */
%SPLITBY(BASE, TRT, 2, SUB, AUCT, AUCI, CMAX, TMAX, KE, THALF)
RUN;

%MERMULT(2, BASE, , , , RATIODAT, SUB)
RUN;

%RATIOCAL(RATIODAT, 2, AUCT, AUCI, CMAX, TMAX, KE, THALF)
RUN;

DATA TCDAT;
SET NEWCONC;
KEEP TRT TIME CONC;
%LET BY=TRT TIME;
%SORTDS(TCDAT, &BY)
RUN;

/* CALCULATE MEAN BLOOD LEVEL AT EACH TIME POINT */
TITLE "&TITLE2";
%MEANCAL(TCDAT, CONC, TRT TIME, CMEANOUT)
RUN;
%*PRINT(CMEANOUT, CMEANOUT)
RUN;

DATA CMEANOUT;
SET CMEANOUT;
DROP _TYPE_ _FREQ_ ;

%TRANSPOS(CMEANOUT, CMEAN, CONC, TRT TIME)
RUN;
%*PRINT(CMEAN, CMEAN)

```

```

RUN;

DATA CMEAN;
SET CMEAN;
RENAME COL4=MEAN
      COL5=SD;
DROP _NAME_ COL1 COL2 COL3;
%*PRINT(CMEAN, &TITLE1)
RUN;

%SPLITBY(CMEAN, TRT, 2, TIME, MEAN, SD, X, X, X, X)
RUN;

%MERGMULT(2, CMEAN, , , , CMEANRAT, TIME)
RUN;
%*PRINT(CMEANRAT, CMEANRAT)
RUN;

%RATIOCAL(CMEANRAT, 2, MEAN, X, X, X, X, X)
RUN;
DATA CMEANRAT;
SET CMEANRAT;
DROP TRT;
%*PRINT(CMEANRAT, &TITLE2)
RUN;

%SORTDS(CMEANRAT, TIME)
RUN;

%LET BY=TRT;
%SORTDS(BASE, &BY)
RUN;

%MACRO MEANCAL(DSN, VARN, BY, MEANOUT);
      PROC MEANS DATA=&DSN NOPRINT;
      VAR &VARN;
      BY &BY;
      OUTPUT OUT=&MEANOUT;
%MEND MEANCAL;

%MACRO univCAL(DSN, VARN, BY, MEANOUT);
      PROC univariate DATA=&DSN NOPRINT;
      VAR &VARN;
      BY &BY;
      OUTPUT OUT=&MEANOUT median=median;
%MEND univCAL;

/* CALCULATE MEAN PHARMACOKINETIC PARAMETERS */
%MEANCAL(BASE, AUCT AUCI CMAX TMAX KE THALF LAUCT LAUCI
LCMAX, TRT, PARMETER)
RUN;

```

```

***** TMAX - MEDIAN DP *****;
%univCAL(BASE, TMAX, TRT, PARMETERtmax)
RUN;

data parameter;
  merge parameter
    parameter_tmax;
  by trt;
run;

data parameter(drop=median);
  set parameter;

  if STAT = "MEAN" then tmax = median;
  if _STAT_ = "STD" then tmax = .;  ** for median tmax, no SD or CV **;
run;

%LET TITLE=SUMMARY OF PHARMACOKINETIC PARAMETERS;
%*PRINT(PARMETER, &TITLE)
RUN;

DATA PARM;
SET PARMETER;
DROP _TYPE_ _FREQ_ ;

PROC TRANSPOSE DATA=PARM OUT=TRSPARM;
VAR AUCT AUCI CMAX TMAX KE THALF LAUCT LAUCI LCMAX;
BY TRT;
RUN;
DATA TRSPARM;
SET TRSPARM;
RENAME _NAME_=NNAME;

%LET BY=NNAME TRT;
%SORTDS(TRSPARM, &BY)
RUN;

***DEV MARCH 23 07** : COMMENT THIS OUT**;
/*
DATA TRSPARM;
SET TRSPARM;
DROP COL1 COL2 COL3;
RENAME COL4=MEAN
      COL5=SD;
RUN;
*/
*** COL1=N COL2=MIN COL3=MAX COL4=MEAN COL5=STD**;
DATA TRSPARM;
SET TRSPARM;
DROP COL1;
RENAME COL2=MIN COL3=MAX COL4=MEAN
      COL5=SD;

```

```

RUN;

%SPLITBY (TRSPARM, TRT, 4, NNAME, MEAN, MIN, MAX, SD, X, X)
RUN;

%MERGMULT (2, TRSPARM, , , , PARMRAT, NNAME)
RUN;

DATA PARMRATS;
SET PARMRAT;
IF %SETLST (NNAME, OR, AUCT, AUCI, CMAX, TMAX, KE, THALF) ;
%RATIOCAL (PARMRATS, 2, MEAN, X, X, X, X, X)
RUN;
DATA PARMRATL;
SET PARMRAT;
IF %SETLST (NNAME, OR, LAUCT, LAUCI, LCMAX, X, X, X) ;
%RATIOLOG (PARMRATL, 2, MEAN, X, X, X, X, X)
RUN;
%ANTILOG (PARMRATL, 2, MEAN, X, X, X, X, X)
RUN;
DATA PKRATIO;
SET PARMRATS PARMRATL;
DROP TRT;

%LET TITLE=TEST MEAN/REFERENCE MEAN RATIO;
%*PRINT (PKRATIO, &TITLE)
RUN;

%ANTILOG (LLSMDAT, 2, LSMEAN, X, X, X, X, X)
RUN;

DATA CIDAT;
SET LLSMDAT LLSMDAT;
KEEP NNAME %LSMENLST (2, LSMEAN)  STDERR %CILST (2) ;

DATA CIDAT;
SET CIDAT;
%RE_NAME (2, LSMEAN, LSM)
RUN;

%SORTDS (CIDAT, NNAME)
RUN;
%*PRINT (CIDAT, CIDAT)
RUN;

%RATIOCAL (CIDAT, 2, LSM, X, X, X, X, X)
RUN;

** DEV **;
** CALCULATE %CV **;
data cmeanrat;
  set cmeanrat;

```

```

    CV1 = round((sd1/mean1)*100, .01);
    CV2 = round((sd2/mean2)*100, .01);
run;

data pkratio;
    set pkratio;

    CV1 = round((sd1/mean1)*100, .01);
    CV2 = round((sd2/mean2)*100, .01);
run;

**DEV TEMPORARILY CLOSED ** MARCH 23 07***;
ods listing close;

** sort order of PK parameters **;
data pkratio;
    set pkratio;

    select (nname);
        when ('AUCT') ordervar=1;
        when ('AUCI') ordervar=2;
        when ('CMAX') ordervar=3;
        when ('TMAX') ordervar=4;
        when ('KE') ordervar=5;
        when ('THALF') ordervar=6;
        when ('LAUCT') ordervar=7;
        when ('LAUCI') ordervar=8;
        when ('LCMAX') ordervar=9;
        otherwise;
    end;
run;

DATA PKRATIO;
    SET PKRATIO;

    IF NNAME IN ("LAUCT", "LAUCI", "LCMAX") THEN DELETE;
RUN;

proc sort
    data=pkratio;
    by ordervar;
run;

data cidat;
    set cidat;

    select (nname);
        when ('AUCT') ordervar=1;
        when ('AUCI') ordervar=2;

```

```

        when('CMAx') ordervar=3;
        when('LAUCT') ordervar=4;
        when('LAUCI') ordervar=5;
        when('LCMAx') ordervar=6;
        otherwise;
    end;
run;

proc sort
    data=cidat;
    by ordervar;
run;

DATA cidat;
    SET cidat;

    IF NNAME IN("AUCT", "AUCI", "CMAx") THEN DELETE;
RUN;

data pkratio;
    set pkratio;

    if nname="AUCT" then units="&aucunit";
    if nname="AUCI" then units="&aucunit";
    if nname="CMAx" then units="&cmaxunit";
    if nname="TMAx" then units="&timeunit";
    if nname="KE" then units="&timeunit.-1";
    if nname="THALF" then units="&timeunit";
run;

data rootmse;
    set fitstat(keep=dependent rootmse);

    if dependent = "LAUCT" then ordervar=1;
    else if dependent="LAUCI" then ordervar=2;
    else if dependent="LCMAx" then ordervar=3;

    if dependent in("LAUCT", "LAUCI", "LCMAx") then output;
run;

proc sort
    data=rootmse;
    by ordervar;
run;

DATA AUCDAT;
SET BASE;
KEEP SUB TRT AUCRATIO;
PROC SORT DATA=AUCDAT;
BY TRT SUB;
RUN;

```

```

/* PROC MEANS ON AUCT/AUCI RATIOS */
PROC MEANS DATA=AUCDAT noprint MAXDEC=2 FW=9;
VAR AUCRATIO;
BY TRT;
OUTPUT OUT=AUCRATIO;
TITLE 'STATISTICS ON AUCT/AUCI RATIOS';
RUN;

PROC TRANSPOSE DATA=aucratio OUT=aucratio1;
VAR aucratio;
BY TRT;
RUN;

data aucratio1;
  length treat $12.;
  set aucratio1;

  rename col1=no col2=mini col3=maxi col4=avg col5=std;
  if trt=1 then treat="TEST";
  else if trt=2 then treat="REFERENCE";
run;

%LET TITLE=AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS;
%PRINT(AUCDAT, &TITLE)
RUN;

PROC PRINT DATA=RATIODAT ROUND noobs;
VAR SUB SEQ %RATLST(2, AUCT, AUCI, CMAX, TMAX, KE, THALF) ;
FORMAT %RATLST(2, AUCT, AUCI, CMAX, TMAX, KE, THALF) 4.2;
TITLE 'TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS';
RUN;

ods listing;

/* PROC MEANS ON TEST/REFERENCE RATIOS */
PROC MEANS DATA=RATIODAT MAXDEC=2 FW=9 noprint;
VAR %RATLST(2, AUCT, AUCI, CMAX, TMAX, KE, THALF) ;
OUTPUT OUT=MEANOUT;
TITLE 'STATISTICS ON THE TEST/REFERENCE RATIOS';
RUN;

DATA CHECKDAT;
SET BASE;

AUCTO_N=OLDAUCT/NEWAUCT;
AUCIO_N=OLDAUCI/NEWAUCI;
CMAXO_N=OLDCMAX/NEWCMAX;
TMAXO_N=OLDTMAX/NEWTMAX;

```

```

OUTPUT;
KEEP SUB TRT PER SEQ AUCTO_N AUCIO_N CMAXO_N TMAXO_N;
LABEL AUCTO_N='AUCT';
LABEL AUCIO_N='AUCI';
LABEL CMAXO_N='CMAX';
LABEL TMAXO_N='TMAX';

%LET TITLE=RATIO OF SPONSOR/REVIEWER CALCULATED PARAMETERS;
%PRINT(CHECKDAT, &TITLE)
RUN;

%LET TITLE=AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS;
%*PRINT(AUCRATIO, &TITLE)
RUN;

/* GOPTIONS DEVICE=EGAL; */      /* GOPTION #1 */
/* GOPTIONS DEVICE=FX85; */      /* GOPTION #2 */
/* GOPTIONS DEVICE=HPLJS2; */    /* GOPTION #3 */
/* GOPTIONS GACCESS='SASGASTD>LPT2:'; */ /* GOPTION #4 */
* GOPTIONS RESET=ALL DEVICE=WIN TARGETDEVICE=WINPRTM ftext=arial; /*
GOPTION
#5 */

ods rtf close;

ods rtf file="&odsfile1" style=mystyle1 bodytitle;

TITLE "MEAN PLASMA CONCENTRATIONS";
proc report data=cmeanrat nowd split='~' box
  style(header)={background=lightorange
                foreground=black}
  style(column)={background=white
                foreground=black};

  column time ("Test (n=&testsub)" mean1 cv1)
            ("Reference (n=&refsub)" mean2 cv2)
            ("Ratio" rmean12);

  define time /order format=8.2 spacing=2 "Time (hr)";
  define mean1 /format=8.2 spacing=2 "Mean (&cmaxunit)";
  define cv1 /format=8.2 spacing=2 "CV%";
  define mean2 /format=8.2 spacing=2 "Mean (&cmaxunit)";
  define cv2 /format=8.2 spacing=2 "CV%";
  define rmean12 /format=8.2 spacing=2 "(T/R)";
run;

footnote "* Tmax values are presented as median, range.";
TITLE "ARITHMETIC MEANS AND RATIOS";
proc report data=pkratio nowd split='\ ' box
  style(header)={background=lightorange
                foreground=black}
  style(column)={background=white
                foreground=black};

```

```

column nname units ("Test" mean1 cv1 min1 max1)
      ("Reference" mean2 cv2 min2 max2)
      ("Ratio" rmean12);

define nname /format=$12. spacing=2 "Parameter";
define units /format=$12. spacing=2 "Unit";
define mean1 /format=8.2 spacing=2 "Mean";
define cv1 /format=8.2 spacing=2 "CV%";
define min1 /format=8.2 spacing=2 "Min";
define max1 /format=8.2 spacing=2 "Max";
define mean2 /format=8.2 spacing=2 "Mean";
define cv2 /format=8.2 spacing=2 "CV%";
define min2 /format=8.2 spacing=2 "Min";
define max2 /format=8.2 spacing=2 "Max";
define rmean12 /format=8.2 spacing=2 "(T/R)";
run;
footnote;

TITLE "LSMEANS AND 90% CONFIDENCE INTERVALS";
proc report data=cidat nowd split='\' box
  style(header)={background=lightorange
                foreground=black}
  style(column)={background=white
                foreground=black};

column nname ("Least Squares Geometric Mean" lsm1 lsm2)
      ("Ratio" rlsm12)
      ("90% Confidence Intervals" lowci12 uppci12);

define nname /format=$12. spacing=2 "Parameter";
define lsm1 /format=8.2 spacing=2 "Test";
define lsm2 /format=8.2 spacing=2 "Reference";
define rlsm12 /format=8.2 spacing=2 "(T/R)";
define lowci12 /format=8.2 spacing=2 "Lower";
define uppci12 /format=8.2 spacing=2 "Upper";
run;

TITLE "ROOT MEAN SQUARE ERROR";
proc report data=rootmse nowd split='\' box
  style(header)={background=lightorange
                foreground=black}
  style(column)={background=white
                foreground=black};

column dependent rootmse;

define dependent /format=$12. spacing=2 "Parameter";
define rootmse /format=8.4 spacing=2 "RMSE";

run;

TITLE "STATISTICS ON AUCTION/AUCI RATIOS";
proc report data=aucratio1 nowd split='\' box
  style(header)={background=lightorange

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```

                                foreground=black}
style (column)={background=white
                                foreground=black};

column treat no avg mini maxi;

define treat /format=$12. spacing=2 "Treatment";
define no /format=8. spacing=2 "n";
define avg /format=8.2 spacing=2 "Mean";
define mini /format=8.2 spacing=2 "Minimum";
define maxi /format=8.2 spacing=2 "Maximum";
run;

ods rtf close;

filename concplot "&plotfile";

goptions reset=all
          device=cgmof97p
          gsfname=concplot
          gsfmode=replace
          ftext=swiss
          rotate=portrait
          targetdevice=winprtm;

TITLE2 "&TITLE3";
TITLE3 "&TITLE4";
TITLE4 "&TITLE5";
TITLE5 "&TITLE6";
FOOTNOTE1 "&FOOTNOT1";
SYMBOL1 C=RED I=JOIN V=dot width=5;
SYMBOL2 C=BLUE I=JOIN V=SQUARE width=5;

AXIS1 label=(a=90 "&label1");

PROC GPLOT DATA=CMEAN UNIFORM;
PLOT MEAN*TIME=TRT / FRAME vaxis=axis1;
LABEL MEAN=("&LABEL1") TIME="&LABEL2";
RUN;
TITLE1;
TITLE2;
TITLE3;
TITLE4;
TITLE5;
TITLE6;

FOOTNOTE1;
FOOTNOTE2;
FOOTNOTE3;
LABEL;
QUIT;

```

4.6.3 Fasting Study Output

FASTING STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	Levels	Values
sub	27	1 2 3 4 5 6 8 9 10 11 12 13 14 16 17 19 20 21 22 23 24 25 26 27 28 29 30
TRT	2	1 2
per	2	1 2
seq	2	1 2

Number of Observations Read	54
Number of Observations Used	54

FASTING STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	5.11947987	0.18283857	9.73	<.0001
Error	25	0.46971951	0.01878878		
Corrected Total	53	5.58919938			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.915959	1.148251	0.137072	11.93748

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.37220004	0.37220004	19.81	0.0002
sub(seq)	25	4.40426704	0.17617068	9.38	<.0001
per	1	0.12293214	0.12293214	6.54	0.0170
TRT	1	0.22008066	0.22008066	11.71	0.0021

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.37220004	0.37220004	19.81	0.0002
sub(seq)	25	4.40426704	0.17617068	9.38	<.0001
per	1	0.11088976	0.11088976	5.90	0.0226
TRT	1	0.22008066	0.22008066	11.71	0.0021

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.37220004	0.37220004	2.11	0.1585

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.12776801	0.03733193	3.42	0.0021

FASTING STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	5.05606678	0.18057381	9.72	<.0001
Error	25	0.46461636	0.01858465		
Corrected Total	53	5.52068315			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.915841	1.141425	0.136326	11.94345

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.36275458	0.36275458	19.52	0.0002
sub(seq)	25	4.35784500	0.17431380	9.38	<.0001
per	1	0.11970430	0.11970430	6.44	0.0178
TRT	1	0.21576290	0.21576290	11.61	0.0022

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.36275458	0.36275458	19.52	0.0002
sub(seq)	25	4.35784500	0.17431380	9.38	<.0001
per	1	0.10793978	0.10793978	5.81	0.0236
TRT	1	0.21576290	0.21576290	11.61	0.0022

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.36275458	0.36275458	2.08	0.1616

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.12650846	0.03712859	3.41	0.0022

FASTING STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	28	5.95338171	0.21262078	8.50	<.0001
Error	25	0.62529411	0.02501176		
Corrected Total	53	6.57867582			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.904951	1.749893	0.158151	9.037759

Source	DF	Type I SS	Mean Square	F Value	Pr > F
seq	1	0.57176665	0.57176665	22.86	<.0001
sub(seq)	25	5.01588898	0.20063556	8.02	<.0001
per	1	0.09491989	0.09491989	3.80	0.0627
TRT	1	0.27080619	0.27080619	10.83	0.0030

Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.57176665	0.57176665	22.86	<.0001
sub(seq)	25	5.01588898	0.20063556	8.02	<.0001
per	1	0.08329320	0.08329320	3.33	0.0800
TRT	1	0.27080619	0.27080619	10.83	0.0030

Tests of Hypotheses Using the Type III MS for sub(seq) as an Error Term					
Source	DF	Type III SS	Mean Square	F Value	Pr > F
seq	1	0.57176665	0.57176665	2.85	0.1038

Parameter	Estimate	Standard Error	t Value	Pr > t
TRT1 VS TRT2	0.14172958	0.04307282	3.29	0.0030

AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

Obs	sub	TRT	AUCRATIO
1	(b) (6)	1	1.00
2		1	0.99
3		1	0.99
4		1	0.99
5		1	1.00
6		1	1.00
7		1	1.00
8		1	0.98
9		1	1.00
10		1	1.00
11		1	1.00
12		1	1.00
13		1	0.99
14		1	0.99
15		1	1.00
16		1	0.99
17		1	0.99
18		1	1.00
19		1	0.99
20		1	0.99
21		1	1.00
22		1	1.00
23		1	0.99
24		1	1.00
25		1	1.00
26		1	0.99
27		1	1.00
28		2	1.00
29		2	0.99
30		2	1.00
31		2	0.99
32		2	1.00
33		2	1.00
34		2	0.99
35		2	0.98
36		2	1.00
37		2	1.00
38		2	1.00
39		2	0.99

Obs	sub	TRT	AUCRATIO
40	(b) (6)	2	0.99
41	(b) (6)	2	0.99
42	(b) (6)	2	1.00
43	(b) (6)	2	0.99
44	(b) (6)	2	0.99
45	(b) (6)	2	1.00
46	(b) (6)	2	0.98
47	(b) (6)	2	1.00
48	(b) (6)	2	1.00
49	(b) (6)	2	0.99
50	(b) (6)	2	0.99
51	(b) (6)	2	1.00
52	(b) (6)	2	1.00
53	(b) (6)	2	0.99
54	(b) (6)	2	1.00

TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

sub	seq	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
(b) (6)	2	1.21	1.20	1.15	1.00	0.99	1.01
	1	0.91	0.91	0.93	1.13	1.28	0.78
	1	0.72	0.72	0.63	1.56	0.80	1.24
	2	1.49	1.48	1.14	1.00	1.03	0.97
	2	1.21	1.21	1.14	1.22	1.18	0.85
	1	1.16	1.16	1.24	0.90	0.88	1.13
	2	1.54	1.54	1.73	0.35	1.18	0.85
	2	1.04	1.03	1.03	1.00	0.96	1.04
	2	0.94	0.94	1.08	0.89	0.89	1.12
	1	1.23	1.23	1.27	1.11	0.98	1.02
	1	0.94	0.94	1.02	2.00	0.96	1.04
	2	1.44	1.43	1.54	1.10	1.24	0.81
	2	1.64	1.64	1.74	1.00	1.10	0.91
	1	0.84	0.84	0.81	0.50	1.24	0.81
	1	1.40	1.40	1.42	0.46	1.06	0.94
	1	1.13	1.13	1.16	1.22	1.05	0.95
	2	0.98	0.97	1.08	1.71	1.09	0.92
	2	1.34	1.34	1.52	1.08	1.09	0.92
	2	1.35	1.35	1.36	1.08	1.07	0.94
	1	0.77	0.77	0.79	0.89	0.87	1.15
	1	1.30	1.30	1.21	1.00	0.98	1.02
	1	1.21	1.21	1.38	1.00	1.32	0.76
	2	1.29	1.28	1.19	1.00	1.09	0.92
	1	0.99	0.99	1.02	1.11	0.89	1.12
	2	1.00	1.00	0.94	0.83	0.95	1.05
	2	1.22	1.21	1.14	1.00	0.91	1.09
	1	1.17	1.17	1.34	1.25	1.00	1.00

RATIO OF SPONSOR/REVIEWER CALCULATED PARAMETERS

Obs	sub	seq	per	TRT	AUCTO_N	AUCIO_N	CMAXO_N	TMAXO_N
1	(b) (6)	2	2	1	1.00	1.00	1	1.00
2	(b) (6)	1	1	1	1.00	1.00	1	1.00
3	(b) (6)	1	1	1	1.00	1.00	1	1.00
4	(b) (6)	2	2	1	1.00	1.00	1	1.01
5	(b) (6)	2	2	1	1.00	1.00	1	1.00
6	(b) (6)	1	1	1	1.00	1.00	1	1.00
7	(b) (6)	2	2	1	1.00	1.00	1	1.00
8	(b) (6)	2	2	1	1.00	1.00	1	1.00
9	(b) (6)	2	2	1	1.00	1.00	1	1.00
10	(b) (6)	1	1	1	1.00	1.00	1	1.00
11	(b) (6)	1	1	1	1.00	1.00	1	1.00
12	(b) (6)	2	2	1	1.00	1.00	1	1.00
13	(b) (6)	2	2	1	1.00	1.00	1	1.00
14	(b) (6)	1	1	1	1.00	1.00	1	1.00
15	(b) (6)	1	1	1	1.00	1.00	1	1.00
16	(b) (6)	1	1	1	1.00	1.00	1	1.00
17	(b) (6)	2	2	1	1.00	1.00	1	1.00
18	(b) (6)	2	2	1	1.00	1.00	1	1.00
19	(b) (6)	2	2	1	1.00	1.00	1	1.00
20	(b) (6)	1	1	1	1.00	1.00	1	1.00
21	(b) (6)	1	1	1	1.00	1.00	1	1.00
22	(b) (6)	1	1	1	1.00	1.00	1	1.00
23	(b) (6)	2	2	1	1.00	1.00	1	1.00
24	(b) (6)	1	1	1	1.00	1.00	1	1.00
25	(b) (6)	2	2	1	1.00	1.00	1	1.00
26	(b) (6)	2	2	1	1.00	1.00	1	1.00
27	(b) (6)	1	1	1	1.00	1.00	1	1.00
28	(b) (6)	2	1	2	1.00	1.00	1	1.00
29	(b) (6)	1	2	2	1.00	1.00	1	1.00
30	(b) (6)	1	2	2	1.00	1.00	1	1.00
31	(b) (6)	2	1	2	1.00	1.00	1	1.00
32	(b) (6)	2	1	2	1.00	1.00	1	1.00
33	(b) (6)	1	2	2	1.00	1.00	1	1.00
34	(b) (6)	2	1	2	1.00	1.00	1	1.00
35	(b) (6)	2	1	2	1.00	1.00	1	1.00
36	(b) (6)	2	1	2	1.00	1.00	1	1.00
37	(b) (6)	1	2	2	1.00	1.00	1	0.89
38	(b) (6)	1	2	2	1.00	1.00	1	1.00
39	(b) (6)	2	1	2	1.00	1.00	1	1.00

Obs	sub	seq	per	TRT	AUCTO_N	AUCIO_N	CMA XO_N	TMAXO_N
40	(b) (6)	2	1	2	1.00	1.00	1	1.00
41	(b) (6)	1	2	2	1.00	1.00	1	1.00
42	(b) (6)	1	2	2	1.00	1.00	1	1.00
43	(b) (6)	1	2	2	1.00	1.00	1	1.00
44	(b) (6)	2	1	2	1.00	1.00	1	1.00
45	(b) (6)	2	1	2	1.00	1.00	1	1.00
46	(b) (6)	2	1	2	1.00	1.00	1	1.00
47	(b) (6)	1	2	2	1.00	1.00	1	1.00
48	(b) (6)	1	2	2	1.00	1.00	1	1.00
49	(b) (6)	1	2	2	1.00	1.00	1	1.00
50	(b) (6)	2	1	2	1.00	1.00	1	1.00
51	(b) (6)	1	2	2	1.00	1.00	1	1.00
52	(b) (6)	2	1	2	1.00	1.00	1	1.00
53	(b) (6)	2	1	2	1.00	1.00	1	1.00
54	(b) (6)	1	2	2	1.00	1.00	1	1.00

4.7 Additional Attachments

4.7.1 DB II Bio Management Meeting Minutes 1/14/2014

DBII Bio Management Meeting Minutes

Meeting Date: Tuesday, January 14, 2014
Meeting Time: 1:00 PM – 2:00 PM
Meeting Location: MM2 4th Floor Conference Room B

Attendees: Ethan Stier, Xiaojian Jiang, Scott Vehovic, Sriram Subramaniam, Parthapratim Chandaroy, Kuldeep Dhariwal, Moheb Makary, Chandra Chaurasia, Minglei Cui, Yi Zhang, Diane Nhu, Nabeel Babaa, and Jessica Kreger

Team Updates:

Kuldeep Dhariwal (Team 9)

ANDA 204403 Rivastigmine Transdermal System

ANDA No.	204403
Drug Product Name	Rivastigmine Transdermal System
Strength(s)	4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr
Applicant Name	Alvogen Pine Brook, Inc.
Address	10 Bloomfield Avenue Building B Pine Brook, NJ 07058
Applicant's Point of Contact	Jasmin Shah
Contact's Telephone Number	(b) (6)
Contact's Fax Number	973.201.1086
Original Submission Date(s)	June 12, 2012
Submission Date(s) of Amendment(s) Under Review	January 22, 2013 (New strength amendment – 13.3 mg/24 hr) December 27, 2013 (ECD Response – COA of RLD)
Reviewer	Jennifer N. Miller, Ph.D.
OUTCOME DECISION	INADEQUATE

Background:

Rivastigmine Transdermal System is an acetylcholinesterase inhibitor indicated for treatment of 1) mild, moderate, (b)(4) dementia of the Alzheimer's type and 2) mild to moderate dementia associated with Parkinson's disease. One patch is applied on intact skin for a 24-hour period and replaced with a new patch every 24 hours.

This application contains the results of a fasting bioequivalence (BE) study comparing a test product, Alvogen Pine Brook, Inc.'s Rivastigmine Transdermal System, 9.5 mg/ 24 hours, to the corresponding reference product, Novartis' Exelon® Patch, 9.5 mg/24 hours.

Plasma concentrations of the parent drug, rivastigmine, were measured. BE should be based on 90% CI of rivastigmine (AUC and Cmax).

For the fasting BE study, three subjects experienced emesis during the study. Two subjects were not included in the statistical analysis (Subjects (b) (6) as they elected to withdraw from the study. Subject (b) (6) experienced 2 episodes of emesis, 1 during Period I (28 hours 45 minutes after dosing, Day 2 at 1325) and 1 during Period II (14 hours 15 minutes after dosing, Day 1 at 2255). Per the firm's protocol, subjects who experienced emesis were analyzed by the bioanalytical laboratory and used in the PK analysis unless they were removed from the study due to safety concerns. Since this subject was not removed from the study due to safety concerns, the PK data was used in the statistical analysis. Those results are below:

Rivastigmine Transdermal System, 9.5 mg/24 hours Fasting Bioequivalence Study No. R10-1307, N=27 (Male=8 and Female=19) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC _{0-t} (pg·hr/mL)	163479.0	143870.9	1.14	106.61	121.11
AUC _∞ (pg·hr/mL)	164348.9	144818.8	1.13	106.51	120.92
C _{max} (pg/mL)	9067.37	7869.17	1.15	107.05	124.02

The firm's protocol states:

“Subjects who experience emesis after patch application will not be removed from the study unless deemed necessary for safety reasons by the clinical staff. Samples from subjects who experience emesis will be analyzed by the Bioanalytical laboratory. However, data from subjects who experience emesis and that have to be removed from the study for safety reasons will not be used in the pivotal pharmacokinetic and statistical analysis.” (Protocol Section 15.3)

Per DB policy for orally administered drugs, Subject (b) (6) vomited should be excluded from the statistical analysis as this subject experienced emesis within the dosing interval of 24 hours. The reviewer performed statistical analysis excluding Subject (b) (6). The 90% CI for C_{max} is 108.18 -125.53%.

However, this is a transdermal product and so vomiting should not influence drug absorption.

Issue:

The firm states that subjects who experience emesis after patch application will not be removed from the study unless deemed necessary for safety reasons by the clinical staff. Since Subject (b) (6) experienced emesis during the dosing interval, should this subject be excluded from statistical analysis? Excluding Subject (b) (6) causes the fasting BE study to fail Cmax (108.18 – 125.53%).

Team's proposal:

The firm's fasting BE study can be accepted as 1) the product is transdermal and 2) the firm's protocol clearly stated that the subject will not be dropped unless deemed necessary for safety reasons.

Rationale for the proposal:

1.



2. For ANDA 200910 Mylan Technologies Inc.'s Norelgestromin and Ethinyl Estradiol Transdermal Patch, a total of 9 subjects experienced emesis during the fasting BE study. All of these subjects were included in the statistical analysis, both by the firm and the reviewer. The reviewer noted that Since the drug product is a transdermal patch (non-oral route of administration), vomiting will not influence drug absorption.
3. Per labeling of EXELON® Patch, most commonly observed adverse reactions (>5% and higher than with placebo) were nausea, vomiting, and diarrhea. These reactions were dose-related. The RLD label states: At higher than recommended doses, Exelon Patch (rivastigmine transdermal system) use is associated with significant gastrointestinal adverse reactions, including nausea, vomiting, diarrhea, anorexia/decreased appetite and weight loss. For this reason, patients administered Exelon Patch should always be started at a dose of 4.6 mg/24 hours and titrated to the maintenance dose of 9.5 mg/24 hours." Therefore, the firm should have enrolled a sufficient number of subjects to account for subjects withdrawn from the study due to emesis. In the current study, the firm enrolled 30 subjects.

Formulation:

Component	Function	Amount in dried matrix / %	Amount mg in 4.6 mg/24 hr Patch Size: 4.6 cm ²	Amount mg in: 9.5 mg/24 hr Patch Size: 9.2 cm ²	Amount mg in: 13.3 mg/24 hr Patch Size: 13.8 cm ²
Active layer, target area weight:	(b) (4)				
Rivastigmine	API	25	6.9 mg	13.8 mg	20.7
(b) (4)					

From Module 3.2.P.1:

Rivastigmine transdermal system (Rivastigmine-TDS) is a matrix patch consisting of two matrix layers. It is available in three strengths, 4.6 mg/24 hr, 9.5 mg/24 hr and 13.3 mg/24 hr. The compositions of all strengths are the same and the only difference is the patch size. The patches are a circular shape.

An impermeable backing liner made from aluminum coated polyester combined with skin colored polyethylene has been chosen to protect the patch from the environment. The patch is situated on a standard release liner with fluoropolymer-coating. This liner is removed prior to application.

After manufacturing each transdermal patch, together with a cover sheet made of polyethylene terephthalate siliconized on one side, is individually packed into a heat-sealed sachet made of paper / polyethylene terephthalate / aluminum / polyacrylonitrile multilaminate to ensure appropriate protection.

RIV-TDS is composed as shown in the following schematic drawing:

- a cover sheet: siliconized polyethylene terephthalate film
- a backing liner: Polyethylene / thermoplastic resin / aluminum coated polyester film
- an active reservoir layer containing the active pharmaceutical ingredient
- an adhesive matrix layer
- a release liner: fluoropolymer coated polyester film



Figure 1 Schematic drawing of newly developed Rivastigmine-TDS

5. The maximum daily dose for Rivastigmine Transdermal System is 13.3 mg/24 hours. Only one transdermal system of either the 4.6 mg/24 hour, 9.5 mg/24 hour or 13.3 mg/24 hours strengths are worn at any given time, according to the package insert for the RLD (Exelon® Patch). Additionally, the patient package insert for the RLD (Exelon® Patch) states that every 24 hours the transdermal system should be removed and a new transdermal system should be applied.
6. The backing liner (b) (4) of the 13.3 mg/24 hour strength is proposed at a level of (b) (4) which exceeds the maximum level in the IIG Database. However, the liner should not be applied to the patients' skin as it is designed to protect the patch from the environment and discarded before the patch is placed on the skin. (This was also noted at the time of filing for the New Strength Amendment and was

acceptable.⁹⁾ Therefore, from a Bioequivalence perspective, the amount of backing liner used in this product is acceptable.

7. The inactive ingredients are within the acceptable IIG limits based on the MDD of 13.3 mg/24 hours.
8. The formulation is **adequate**.

Discussion:

After the presentation of the key issues, the only option discussed was that since this is a transdermal product, vomiting has no affect on absorption of drug, therefore the subject should not be dropped.

Question:

Does the management agree that Subject (b) (6) should not be excluded from statistical analysis even though the subject experienced emesis during the dosing interval?

Management Decision:

For transdermal products, subjects who experience emesis during the dosing interval do not need to be dropped from statistical analysis.

⁹ ANDA 204403 DARRTS REV-RPM-03(Filing Review); Submit Date: 5/20/2013

NOTE FOR RPM: This application is pending an OSI inspection of the Analytical site.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 204403

APPLICANT: Alvogen Pine Brook, Inc.

DRUG PRODUCT: Rivastigmine Transdermal System,
4.6 mg/24 hr, 9.5 mg/24 hr, and
13.3 mg/24 hr

The Division of Bioequivalence (DB) II has completed its review and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.8 Outcome Page

COMPLETED ASSIGNMENT FOR 204403 ID: 21411

Reviewer: Miller, Jennifer

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Rivastigmine Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
21411	6/12/2012	Bioequivalence Study (REGULAR)	Fasting Study	1	1
21411	6/12/2012	Other (REGULAR)	Dissolution-Based BE (eg MR products)	2	2
				Total:	3

COMPLEXITY POINTS

ANDA: 204403

BE Study Fasting	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
<i>Fasting Study Total</i>	<i>3</i>
Waiver Request	
Strength 1	0.5
Strength 2	0.5
<i>Waiver Total</i>	<i>1</i>
Total	4

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JENNIFER N MILLER
02/05/2014

KULDEEP R DHARIWAL
02/06/2014

ETHAN M STIER
02/07/2014

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	204403
Drug Product Name	Rivastigmine Transdermal System
Strength (s)	4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr
Applicant Name	Alvogen Pine Brook, Inc.
Applicant Address	10 Bloomfield Avenue Building B Pine Brook, NJ 07058
US Agent Name and the mailing address	Jasmine Shah – VP, Regulatory and Medical Affairs
US Agent's Telephone Number	(b) (6)
US Agent's Fax Number	973-201-1086
Original Submission Date(s)	June 12, 2012
Submission Date(s) of Amendment(s) Under Review	November 11, 2013
First Generic	No
Reviewer	Saeid Raofi
Study Number (s)	R10-1307
Study Type (s)	PK study (relative bioavailability and adhesive properties of a transdermal system)
Strength(s)	9.5 mg / 24 Hours Patch
Clinical Site	Cetero Research
Clinical Site Address	4801 Amber Valley Parkway Fargo, ND 58104, USA
Analytical Site	(b) (4)
Analytical Address	
Dissolution Method	Correct
OVERALL REVIEW RESULT (Supporting Document 14)	INADEQUATE

Review of a Dissolution Amendment

1 EXECUTIVE SUMMARY

This is a dissolution amendment review.

In the deficiency letter of October 8, 2013 (ANDA 204403 – DARRTS: COR-ANDE-09 (Bio Dissolution Deficiencies) the firm was asked to acknowledge the following DB II recommended dissolution method and specifications:

Medium:	0.9% NaCl
Volume:	500 mL
Apparatus:	Modified USP Type VI (Cylinder)
Speed:	50 rpm
Temperature:	32 °C

Specifications:

1 hour:	(b) (4)
2 hours:	(b) (4)
4 hours:	(b) (4)
9 hours:	(b) (4)
24 hours:	(b) (4)

In the current submission, the firm has accepted the Agency's proposed specifications for the 1 hr, 2 hr, 4 hr, and 9 hr time points. However, the firm is requesting that no upper limit be specified at the 24 hour time point, and is proposing a dissolution specification of NLT (b) (4) at the 24 hour time point.

The firm's rationale for eliminating the upper limit of (b) (4) % in the DB II recommended dissolution specification at the 24 hour time point (b) (4) % is that a batch with an assay value close to the upper limit of the (b) (4) % assay acceptance range will have more than (b) (4) % release at the 24 hour time point. In support of its rationale, the firm has submitted summary dissolution data on a new experimental batch of the 9.5 mg/24 hours strength (lot # P0022AK_319RIUTDS) with assay value of (b) (4) % showing average percent release of (b) (4) % (range: (b) (4) %) at 24 hours. The firm also submitted summary dissolution data on another new experimental batch of the 9.5 mg/24 hours strength (lot # P0022AK_320RIUTDS) with assay value of (b) (4) % showing average percent release of (b) (4) % (range: (b) (4) %) at 24 hours.

Per DB policy, dissolution specifications are set based on the data obtained on fresh bio lots and are not modified based on development, scale up or stability batch data. The above DB II recommended dissolution method and specifications were developed in consultation with the DB II Dissolution Focal Point (please see Additional Attachment – Item 1) based on the data submitted in the original application on bio-lot.

Specifying a range for percent dissolved at the 24 hour time point is consistent with *USP Chapter 24 – Table 1* recommendations for setting dissolution specifications for

transdermal systems. Dissolution data from experimental batches that have assay values near or above the top end of assay acceptance range is not adequate justification for eliminating the upper limit for dissolution specification at the 24 hour time point. After consulting the DB II Dissolution Focal Point on acceptability of the firm's request to eliminate the upper limit at the 24 hour time point, the DB II management has concluded that the upper limit at the 24 hour time point can not be eliminated. However, the DB II has revised the upper limit at the 24 hour time point from (b) (4)%. The following revised dissolution specifications should be communicated to the firm (please see Additional Attachment – Item 2).

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications:

1 hour: (b) (4)
2 hours: (b) (4)
4 hours: (b) (4)
9 hours: (b) (4)
24 hours: (b) (4)

The firm will be requested to acknowledge the above dissolution method and revised dissolution specifications.

The firms dissolution testing is incomplete.

2 REVIEW OF SUBMISSION

In the deficiency letter of October 8, 2013 (ANDA 204403 – DARRTS: COR-ANDA-09(Bio Dissolution Deficiencies)) the firm was informed of the following deficiency.

DB deficiency:

The DB II finds your proposed release specification of (b) (4) % at the 4-hour time point acceptable. However, your proposed release specification of NLT (b) (4) % at the 24-hour time point is not acceptable. Per USP Chapter <1092>, the DBII makes allowances for assay and content uniformity ranges. However, this chapter further states that acceptance criteria including test times are usually established on the basis of an evaluation of the dissolution profile data. Therefore, based on your submitted data, and in accordance with USP Chapter <1092> and Chapter 724, Table 1, the DBII is recommending a release range of (b) (4) % at the 24-hour time point. In the opinion of the DBII, this specification adequately captures the terminal release profile of the test product and ensures better quality control against any possible overage in the future test product batches. Your rationale for a dissolution specification of NLT (b) (4) % at the 24-hour time point is inadequate. Please provide adequate justification for your proposed release specification of NLT (b) (4) % at the 24-hour time point. Alternatively, you may acknowledge the following DB II-recommended dissolution method and revised DB II-recommended release specifications:

Medium:	0.9% NaCl
Volume:	500 mL
Apparatus:	Modified USP Type VI (Cylinder)
Speed:	50 rpm
Temperature:	32 °C

Specifications:

1 hour:	(b) (4)
2 hours:	(b) (4)
4 hours:	(b) (4)
9 hours:	(b) (4)
24 hours:	(b) (4)

Firm's response:

Alvogen accepts the Agency's proposed specification limits for the 1 hr, 2 hr, 4 hr, and 9 hr time points. In our Amendment (Sequence 0011) submitted on June 20, 2013 Alvogen proposed a 24 hr time point specification of NLT (Not Less Than) (b) (4) % based on the finished product assay specification of (b) (4) % of labeled content) and the Content Uniformity test, which allows single patches to have an individual assay level of (b) (4) % with an AV of NMT (b) (4).

Additional experiments have been performed to investigate the influence of assay of the drug product on the dissolution profile. Specifically on batches with rivastigmine content

at the upper limit of the assay specification. Two laboratory batches were manufactured with an assay value of (b) (4) % (batch code: P0022AK_319RruTDS) and (b) (4) % (batch code: P0022AK_320RIUTDS) and dissolution testing was performed utilizing the finished product release method (FDA Proposed Method). The following tables summarize the released amounts of rivastigmine for the specified time points in [%].

Table 1: Drug release from P0022AK_319RIUTDS, 9.2 cm 2, Assay (b) (4) %, Manufacture: Oct 2013, Month of testing: Oct 2013

N=12	1 h	2h	4h	9h	24 h
Mean [%]	22.81	38.82	62.15	89.86	104.39
Min[%]	(b) (4)				
Max[%]	(b) (4)				

Table 2: Drug release from P0022AK_320RIUTDS, 9.2 cm\ Assay (b) (4) %, Manufacture: Oct 2013, Month of testing: Oct 2013

N=6	1 h	2h	4h	9h	24 h
Mean [%]	22.25	38.30	62.20	93.19	111.20
Min[%]	(b) (4)				
Max[%]	(b) (4)				

A nearly full quantitative release of rivastigmine was observed after 24 hours for both batches, which exceeded FDA recommended limit at 24 hours. The data also demonstrate, that assay of the drug product has a primary impact on the amount released at the end of the dissolution test, whereas the released quantities at early time points (up to 4 hours) are not affected by a higher batch assay.

It is observed that a product batch with an assay value of more than (b) (4) % fails to meet the dissolution specification at both the 9 hour and 24-hour time points. While a drug product batch with an assay value of (b) (4) % (within currently proposed assay specification limit) will exceed the FDA recommended specification at the end of the dissolution test with a mean of (b) (4) % released (24-hour time point). Therefore, considering the dependency of the released quantity at the end of the dissolution and assay of the drug product; Alvogen proposes that no upper limit specification is necessary for the dissolution test since the Assay and Content Uniformity tests are providing adequate controls for potency.

However, it is agreed that the lower limit for dissolution at the 24 hour time point should be lifted from (b) (4) % to (b) (4) % to allow a better control of the drug products quality.

In conclusion, the applicant proposes the following drug product specification for dissolution:

Table 3: Comparison of Current Specification and FDA Recommended Specification for Dissolution

	I hour	2 hours	4 hours	9 hours	24 hours
FDA recommended specification (stated range)	(b) (4)				
Proposed specification (stated range)					

This Bioequivalence Amendment has been prepared in accordance with 21 CFR 314.94 and is being submitted via the Electronic Secured Gateway (ESG). The content of the application was verified to be virus free using Trend Micro Office Scan November 11, 2013.

This concludes our response to the Agency's request of 10/08/2013. Should you have any questions concerning this Amendment, please do not hesitate to contact the undersigned, Mr. Jasmine Shah, via telephone at (b) (6) via fax at 973-201-1086 or via his email atjasmine.shah@alvogen.com.

Reviewer's Comment:

The test product's assay value acceptance range is (b) (4) % to (b) (4) % and assay values for the 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr are (b) (4) %, (b) (4) %, and (b) (4) % respectively.

The firm's rationale for eliminating the upper limit of (b) (4) % in the DB II recommended dissolution specification at the 24 hour time point (b) (4) % is that a batch with an assay value close to the upper end of the (b) (4) % assay acceptance range will have more than (b) (4) % release at the 24 hour time point.

(b) (4)

USP Apparatus: VI (cylinder)
Speed: 50 rpm
Medium: 0.9% NaCl
Volume: 500 mL
Temperature: 32°C ± 0.5°C

Specifications:

1 hr: (b) (4)
2 hr: (b) (4)
4 hr: (b) (4)
9 hr: (b) (4)
24 hr: (b) (4)

In the case of ANDA (b) (4) it is noted that at the 24 hour time point a range ((b) (4)%) has been specified and the firm acknowledged the above dissolution specifications (ANDA (b) (4) – DARRTS: REV-BIOEQ-01(General Review) – 4/10/2012)).

In the case of the current application, the following dissolution method and specifications were developed in consultation with the DB II Dissolution Focal Point (please see Additional Attachment – Item 1) and communicated to the firm in the deficiency letter of October 8, 2013 (ANDA 204403 – DARRTS: COR-ANDA-09 (Bio Dissolution Deficiencies):

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications:

1 hour: (b) (4)
2 hours: (b) (4)
4 hours: (b) (4)
9 hours: (b) (4)
24 hours: (b) (4)

The DB II Dissolution Focal Point noted that a percent dissolved range was being specified at the 24 hour time point to accommodate Acceptance Table 1 in USP Chapter 724.

Specifying a range for percent dissolved at the 24 hour time point is consistent with USP Chapter 24 recommendations for setting dissolution specifications for transdermal systems. Dissolution data from experimental batches that have assay values near or above the top end of assay acceptance range is not adequate justification for eliminating the upper limit of (b) (4)% for the dissolution specification at the 24 hour time point. Per DB policy, dissolution specifications are set based on the data obtained on fresh bio lots and are not modified based on development, scale up or stability batch data. The FDA recommended dissolution method and specifications communicated to the firm in the deficiency letter of October 8, 2013 were based on the submitted dissolution data in the original submission of June 12, 2012 on lot # C0002AL0AT (4.6 mg/24 hr) and lot # C0004AL0AU (9.5 mg/24 hr), and January 22, 2013 on lot # C0014AL0BC (13.3 mg/24 hr). In accordance with USP Chapter 24 – Table 1, a range was specified for percent dissolved at the 24 hour time point. After consulting the DB II Dissolution

Focal point on acceptability of the firm's request to eliminate the upper limit of (b) (4) % at the 24 hour time point, the DB II management has concluded that the upper limit at the 24 hour time point can not be eliminated. However, the DB II has revised the upper limit at the 24 hour time point from (b) (4). The following revised dissolution specifications should be communicated to the firm (please see Additional Attachment – Item 2).

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications:

1 hour: (b) (4)
2 hours: (b) (4)
4 hours: (b) (4)
9 hours: (b) (4)
24 hours: (b) (4)

3 DEFICIENCY COMMENTS

The firm proposed that no upper limit specification is necessary for the dissolution test since the Assay and Content Uniformity tests are providing adequate controls for potency based on observations from data on development batches. It is noted that the dissolution specifications are set based on the data obtained on fresh bio lots and are not modified based on development, scale up or stability batch data and recommendation of a range at the 24 hour time point is in accordance with USP Chapter 24 – Table 1. Therefore, based on the submitted dissolution data in the original submission of June 12, 2012 on lot # C0002AL0AT (4.6 mg/24 hr) and lot # C0004AL0AU (9.5 mg/24 hr), and January 22, 2013 on lot # C0014AL0BC (13.3 mg/24 hr), the DB II recommends the following revised dissolution method and specifications:

Medium:	0.9% NaCl
Volume:	500 mL
Apparatus:	Modified USP Type VI (Cylinder)
Speed:	50 rpm
Temperature:	32 °C

Specifications:

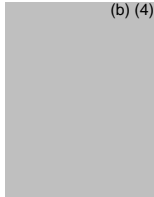
1 hour:

2 hours:

4 hours:

9 hours:

24 hours:



The firm is requested to acknowledge the above dissolution method and specifications.

4 RECOMMENDATIONS

The firm's dissolution testing comparing Rivastigmine Transdermal System 4.6 mg/24hr (lot # C0002AL0AT), 9.5 mg/24hr (lot # C0004AL0AU), and 13.3 mg/24 hr (lot # C0014AL0BC) to Novartis Pharmaceuticals Corporation's Exelon[®] Patch, 4.6 mg/24hr (lot # 1200 BA), 9.5 mg/24hr (lot # 1401B), and 13.3 mg/24 hr (lot # 2302A BA) is incomplete due to the deficiency listed above.

5 ADDITIONAL ATTACHMENT

5.1 Item 1

From: Anand, Om
Sent: Thursday, September 19, 2013 9:04 AM
To: Stier, Ethan
Cc: Anand, Om; Mahadevan, Chitra
Subject: RE:

Ethan:

Technically, it ((b) (4) % range) is not wrong but it creates unnecessary confusion. I am in opinion that we can follow our more conventional approach as the starting point i.e. we can set a specification of NLT ((b) (4) % for the last time point. Now to accommodate Acceptance Table 1 in USP Chapter 724, we can put it in range form i.e. ((b) (4) %. We can also tell the firm that we are establishing range as per USP Chapter 724.

After looking at the data, I agree with the following specifications:

1 hr: ((b) (4))
2 hr: ((b) (4))
4 hr: ((b) (4))
9 hr: ((b) (4))
24 hr: ((b) (4))

Please let me know if you need any clarification/information.

Thank you

Om

From: Stier, Ethan
Sent: Wednesday, September 18, 2013 6:42 PM
To: Anand, Om; Mahadevan, Chitra
Subject:

Hi Om

Can you double check the specification for this? Specifically the fact that it's greater than ((b) (4) %? Y'm assuming it has to do with the fact that there is more drug in the dosage form than the label amount that will be delivered?

5.2 Item 2

Hi, Chandra:

Based on discussion with Ethan and Om, we came to a conclusion to adopt Om's recommended specifications:

Specifications:

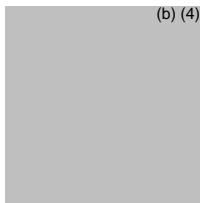
1 hour:

2 hours:

4 hours:

9 hours:

24 hours:



Would you please revise the review accordingly and insert the e-mail?

Thank you so much!
Xiaojian

From: Anand, Om
Sent: Tuesday, December 10, 2013 6:59 AM
To: Jiang, Xiaojian
Cc: Anand, Om; Stier, Ethan
Subject: RE: rivastigmine TDS dissolution specification, 204403

Xiaojian:

A few observations:

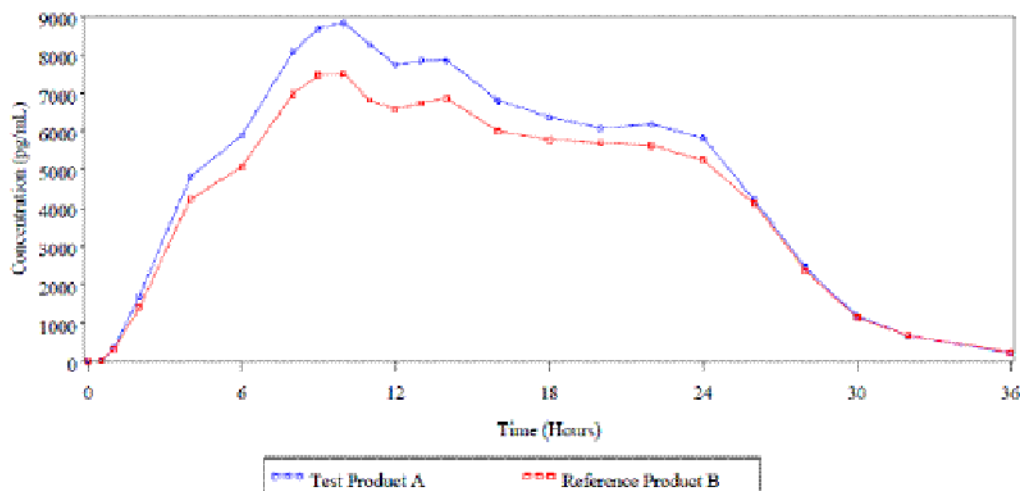
1. The BE study is a borderline study w.r.t. both Cmax and AUC.

AUC _{0-t} (pg-hr/mL)	12.004	11.877	163464.95	143876.95	113.61	(106.60, 121.09)
AUC _{0-inf} (pg-hr/mL)	12.010	11.883	164334.80	144824.77	113.47	(106.50, 120.90)
C _{max} (pg/mL)	9.112	8.971	9067.37	7869.17	115.23	(107.05, 124.02)

*Geometric means are based on the exponential of LSM of ln-transformed values.

2. There is no direct in vivo relation to the in vitro performances. Please note that the in vitro release of the test product at 4 hours is approximately $\frac{(b)}{(4)}$ % and that of reference is approximately $\frac{(b)}{(4)}$ % i.e. RLD is 13% > than the test. However, the figure below shows that from 4-6 hours the plasma levels of the test product are above the reference. This also indicates that the test and reference product release mechanisms are different and it is not the best idea to completely follow the RLD style specifications. Also, the test batch should perform consistently as the bio-batch.

Figure 11.4.1 Mean Plasma Concentration (0 – 36 hours) for Rivastigmine (N = 27)



- 3 As per information provided by you the test is designed to be 1.5 mg/cm² whereas the RLD is designed to be 1.8 mg/cm² i.e. even though initially there is low concentration gradient from the test, at 4 hours we can see the in vivo release is much higher this indicates at two potential differences i.e. a. the test is releasing faster on skin and b.) formulation differences.

- 4 The potency of the bio-batch of the test product is (b) (4)%. Please note that with increase in potency (to (b) (4)%) of the batches there is no significant affect on in vitro dissolution until 4 hours. However, only 9 hours and 24 hours capture these differences. There is no data to show the affect of these differences on bio, however in my opinion, the amount of drug available for absorption in between the patch and the skin can affect the bioavailability and hence BE, more so since this is a borderline product. The question is, how can the batches which are releasing approximately (b) (4)% more than the bio-batch (at 24 hours) can be deemed bioequivalent to the bio-batch. Therefore, the specifications should be based on the bio-batch data only.

- 5 Please also note that with potency of (b) (4)% the bio-batch is releasing from (b) (4)% at 24 hours i.e. 5 to 14 % less than the mean assay, whereas the new batches are releasing similar to the mean assay (mean dissolution of (b) (4) and (b) (4) for (b) (4) and (b) (4)% assay respectively). Further, the firm is proposing the assay limit from (b) (4) (b) (4)% and content uniformity limit from (b) (4)%. I am not sure about the rationale behind these limits, more so since this is a borderline study.

Based on above observations, I am in opinion that the 9 hour and 24 hour time points are very important. The 24-hour time point release demonstrates that

with change in assay, there is change in the dissolution and therefore we should keep this way. By changing it to NLT style, we miss the important information and control.

I am also in opinion that the Division of Chemistry should be consulted to discuss the limits of the assay and the content uniformity. If the assay limit of (b) (4) % is accepted then, based on bio-batch data, I recommend the following specifications:

Specifications:

1 hour:

2 hours:

4 hours:

9 hours:

24 hours:



I am further in opinion that if the assay's upper limit is reduced to (b) (4) % then the 24 hour specifications should be reduced to (b) (4) %.

Please let me know if you have any further questions or need further discussion.

Thank you

Om

From: Jiang, Xiaojian
Sent: Monday, December 09, 2013 11:47 PM
To: Anand, Om
Cc: Stier, Ethan
Subject: rivastigmine TDS dissolution specification, 204403

Hi, Om:

I provided my proposal in the order of my preference and data as follows. Please let me know which option that you like.

Proposal:

I think firm's request is reasonable (please see below).

Option 1): remove specification at 24 hrs: a) the drug release in vivo is only 66% of the label claim b) the RLD specification is covering (b) (4) % at 7 hrs, c) at 9 hr, (b) (4) % in covered for the test product.

Option 2) recommend NLT (b) (4) % as we usually do for ER product. We can set up level 2 and level 3 specifications similarly as ranges.

Level 1:
 6 patches are tested and each patch complies with the specification:
 1 h: (b) (4)
 4 h: (b) (4)
 24 h: (b) (4)

Level 2:
 6 additional patches are tested and the mean of 12 patches (Level 1 + Level 2) must comply with the Level 1 specification, above and no patch is allowed to be outside of the following specification:
 1 h: (b) (4)
 4 h: (b) (4)
 24 h: (b) (4)

Level 3:
 12 additional patches are tested and the mean of 24 patches (Level 1 + Level 2 + Level 3) must comply with the above mentioned Level 1 specification. Maximum of two patches are allowed to be outside of the following specification:
 1 h: (b) (4)
 4 h: (b) (4)
 24 h: (b) (4)

and no patch is allowed to be outside of the following specification:
 1 h: (b) (4)
 4 h: (b) (4)
 24 h: (b) (4)

Option 3) recommend (b) (4)%, I do not like this also.

Background:

We recommended the following specifications:

Specifications:

1 hour: (b) (4)
 2 hours: (b) (4)
 4 hours: (b) (4)
 9 hours: (b) (4)
 24 hours: (b) (4)

The firm requested two times to change specification at 24 hrs to NLT (b) (4)%. The reason is that when the potency of the drug is above (b) (4)%, the % release at 24 hours exceed (b) (4)% (see the below data):

Assay (b) (4) %

N=12	1 h	2h	4h	9h	24 h
Mean [%]	22.81	38.82	62.15	89.86	104.39
Min [%]	(b) (4)				
Max [%]	(b) (4)				

Assay (b) (4) %

N=6	1 h	2h	4h	9h	24 h
Mean [%J	22.25	38.30	62.20	93.19	111.20
Min[%]	(b) (4)				
Max[%]					

Original data for the test are as follows:

0	1	2	4	7	9	12	24

Mean	0	23.53	38.01	57.69	73.72	79.59	84.64	90.60	(b) (4)
Range	(b) (4)								
%CV	-	3.09	1.72	1.68	1.82	2.07	2.03	1.58	

The RLD specification is :

2hr: (b) (4)
 4 hr: (b) (4)
 7hr: (b) (4)

The original data for the reference:

Mean	0	40.10	56.34	69.83	78.10	81.04	84.06	89.64	(b) (4)
Range	(b) (4)								
%CV	-	0.69	0.80	0.86	0.90	0.92	0.98	1.05	

The content in the dosage units is greater than the actual dose per 24 hrs:

Dose (mg/24hr)	Test product		Reference product	
	Size (cm ²)	Rivastigmine Content (mg)	Size (cm ²)	Rivastigmine Content (mg)
4.6	4.6	6.9	5	9
9.5	9.2	13.8	10	18

The dissolution was

based on the label claim (1.5 mg/cm²). Only (b) (4) of drug penetrate the skin over the 24 hrs. As stated in OCP review of the RLD,
“The in vitro release rate in 7 hours exceeds the in vivo delivery rate observed in 24 hours. From this argument, it can be concluded that the rates of drug dissolution in the in-vitro release test are not comparable to rates of in-vivo dermal absorption. Therefore, in vitro dissolution in this case is a quality control test.”

BIOEQUIVALENCE DEFICIENCY

ANDA: 204403
APPLICANT: Alvogen Pine Brook, Inc.
DRUG PRODUCT: Rivastigmine Transdermal System; 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr

The Division of Bioequivalence II (DB II) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence study and waiver requests will be conducted later. The following deficiency has been identified:

You proposed that no upper limit specification is necessary for the dissolution test since the Assay and Content Uniformity tests are providing adequate controls for potency based on observations from data on development batches. However, please note that the dissolution specifications are set based on the data obtained on fresh bio lots and are not modified based on development, scale up or stability batch data and recommendation of a range at the 24 hour time point is in accordance with USP Chapter 24 - Table 1. Therefore, based on the submitted dissolution data in the original submission of June 12, 2012 on lot # C0002AL0AT (4.6 mg/24 hr) and lot # C0004AL0AU (9.5 mg/24 hr), and January 22, 2013 on lot # C0014AL0BC (13.3 mg/24 hr), the DB II recommends the following revised dissolution method and specifications:

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications:

1 hour:  (b) (4)
2 hours: 
4 hours: 
9 hours: 
24 hours: 

Please acknowledge the above dissolution method and specifications.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA: 204403; Applicant: Alvogen Pine Brook, Inc.; Drug Product: Rivastigmine
Transdermal System; 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr

Productivity Data

Completed Assignment for 204403 ID: 21223

Reviewer: Raofi, Saeid

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Rivastigmine Transdermal System

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
21223	11/11/2013	Dissolution Data (REGULAR)	Dissolution Amendment	1	1
				Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Dissolution Study	
Dissolution Amendment	1
Dissolution Amendment	0
Total	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SAEID RAOFI
12/16/2013

CHANDRA S CHAURASIA
12/16/2013

ETHAN M STIER
12/19/2013

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	204403
Drug Product Name	Rivastigmine Transdermal System
Strength (s)	4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr
Applicant Name	Alvogen Pine Brook, Inc.
Applicant Address	10 Bloomfield Avenue Building B Pine Brook, NJ 07058
US Agent Name and the mailing address	Jasmine Shah – VP, Regulatory and Medical Affairs
US Agent’s Telephone Number	(b) (6)
US Agent’s Fax Number	973-201-1086
Original Submission Date(s)	June 12, 2012
Submission Date(s) of Amendment(s) Under Review	June 20, 2013
First Generic	No
Reviewer	Saeid Raofi
Study Number (s)	R10-1307
Study Type (s)	PK study (relative bioavailability and adhesive properties of a transdermal system)
Strength(s)	9.5 mg / 24 Hours Patch
Clinical Site	Cetero Research
Clinical Site Address	4801 Amber Valley Parkway Fargo, ND 58104, USA
Analytical Site	(b) (4)
Analytical Address	
Dissolution Method	Correct
OVERALL REVIEW RESULT	INADEQUATE

Addendum to Review

1 EXECUTIVE SUMMARY

Upon completion of the review of the dissolution amendment dated June 20, 2013 the DB II recommended the following dissolution method and specifications (ANDA 204403 – DARRTS: REV-BIOEQ-02(Dissolution Review)):

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications:

1 hr:
2 hr:
4 hr:
9 hr:
24 hr:



Subsequent to completion and finalization of the above mentioned review, a consult was requested from the DB II Dissolution Focal Point on the recommended dissolution specification at the 24 hour time point (Please see Additional Attachment).

In accordance with the DB II Dissolution Focal Point recommendation, the DB II is revising its recommended dissolution specification at the 24 hour time point. The revised DB II recommended dissolution method and specifications are as follows:

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications:

1 hr:
2 hr:
4 hr:
9 hr:
24 hr:



A revised letter indicating the above specifications is attached to this addendum.

2 ADDITIONAL ATTACHMENT

From: Anand, Om
Sent: Thursday, September 19, 2013 9:04 AM
To: Stier, Ethan
Cc: Anand, Om; Mahadevan, Chitra
Subject: RE:

Ethan:

Technically, it (b) (4) % range) is not wrong but it creates unnecessary confusion. I am in opinion that we can follow our more conventional approach as the starting point i.e. we can set a specification of NLT (b) (4) % for the last time point. Now to accommodate Acceptance Table 1 in USP Chapter 724, we can put it in range form i.e. (b) (4)%. We can also tell the firm that we are establishing range as per USP Chapter 724.

After looking at the data, I agree with the following specifications:

1 hr: (b) (4)
2 hr: (b) (4)
4 hr: (b) (4)
9 hr: (b) (4)
24 hr: (b) (4)

Please let me know if you need any clarification/information.

Thank you

Om

From: Stier, Ethan
Sent: Wednesday, September 18, 2013 6:42 PM
To: Anand, Om; Mahadevan, Chitra
Subject:

Hi Om

Can you double check the specification for this? Specifically the fact that it's greater than (b) (4) %? Y'm assuming it has to do with the fact that there is more drug in the dosage form then the label amount that will be delivered?

BIOEQUIVALENCE DEFICIENCY

ANDA: 204403
APPLICANT: Alvogen Pine Brook, Inc.
DRUG PRODUCT: Rivastigmine Transdermal System; 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr

The Division of Bioequivalence II (DB II) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence study and waiver requests will be conducted later. The following deficiency has been identified:

The DB II finds your proposed release specification of (b) (4) - (b) (4)% at the 4-hour time point acceptable. However, your proposed release specification of NLT (b) (4)% at the 24-hour time point is not acceptable. Per USP Chapter <1092>, the DB II makes allowances for assay and content uniformity ranges; however, this chapter further states that acceptance criteria including test times are usually established on the basis of an evaluation of the dissolution profile data. Therefore, based on your submitted data, and in accordance with USP Chapter <1092> and Chapter 724, Table 1, the DB II is recommending a release range of (b) (4)% at the 24-hour time point. In the opinion of the DB II, this specification adequately captures the terminal release profile of the test product and ensures better quality control against any possible overage in the future test product batches. Your rationale for a dissolution specification of NLT (b) (4)% at the 24-hour time point is inadequate. Please provide adequate justification for your proposed release specification of NLT (b) (4)% at the 24-hour time point. Alternatively, you may acknowledge the following DB II-recommended dissolution method and revised DB II-recommended release specifications:

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications:

1 hr:  (b) (4)
2 hr: 
4 hr: 
9 hr: 
24 hr: 

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA: 204403; Applicant: Alvogen Pine Brook, Inc.; Drug Product: Rivastigmine
Transdermal System; 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr

3 OUTCOME PAGE

Completed Assignment for 204403 ID: 20762

Reviewer: Raofi, Saeid

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Rivastigmine Transdermal System

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
20762	6/20/2013	Other (REGULAR)	Addendum	0	0
				Total:	0

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Addendum	
Study Addendum (modifying recommended dissolution specifications)	0
<i>Study Addendum Total</i>	<i>0</i>

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SAEID RAOFI
09/23/2013

CHANDRA S CHAURASIA
09/23/2013

ETHAN M STIER
09/24/2013

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	204403
Drug Product Name	Rivastigmine Transdermal System
Strength (s)	4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr
Applicant Name	Alvogen Pine Brook, Inc.
Applicant Address	10 Bloomfield Avenue Building B Pine Brook, NJ 07058
US Agent Name and the mailing address	Jasmine Shah – VP, Regulatory and Medical Affairs
US Agent's Telephone Number	(b) (6)
US Agent's Fax Number	973-201-1086
Original Submission Date(s)	June 12, 2012
Submission Date(s) of Amendment(s) Under Review	June 20, 2013
First Generic	No
Reviewer	Saeid Raofi
Study Number (s)	R10-1307
Study Type (s)	PK study (relative bioavailability and adhesive properties of a transdermal system)
Strength(s)	9.5 mg / 24 Hours Patch
Clinical Site	Cetero Research
Clinical Site Address	4801 Amber Valley Parkway Fargo, ND 58104, USA
Analytical Site	(b) (4)
Analytical Address	(b) (4)
Dissolution Method	Correct
OVERALL REVIEW RESULT	INADEQUATE

Review of a Dissolution Amendment

1 EXECUTIVE SUMMARY

This is a dissolution amendment review.

Upon review of the dissolution data submitted in the original submission of June 12, 2012 and two dissolution amendments submitted on April 11, 2013 and May 2, 2013^{1,2}, the DB II found that the firm has conducted acceptable regulatory dissolution testing using the following FDA recommended dissolution method:

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

However, the firm-proposed release specifications were found not acceptable. Based on the submitted data, in the deficiency letter of May 23, 2013³ the DB II recommended that the firm acknowledge the following release specifications for all strengths of the test product (4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr):

1 hr: (b) (4)
2 hr: (b) (4)
4 hr: (b) (4)
9 hr: (b) (4)
24 hr: (b) (4)

In its response in the current submission dated June 20, 2013, the firm has acknowledged the dissolution method mentioned above and accepted the DB II recommended release specifications at the 1 hour, 2 hour, and 9 hour time points. However, the firm is proposing release specifications of (b) (4)% and NLT (b) (4)% at the 4 hour and 24 hour time points, respectively.

The DB II finds the firm proposed release specification of (b) (4)% at the 4 hour time point acceptable. However; the DB II does not find the specification of NLT (b) (4)% at the 24 hour time point acceptable at this point. The DB II acknowledges the firm's rational that according to USP Chapter <1092> allowance needs to be made for assay and content uniformity ranges. However, USP Chapter <1092> also states that acceptance criteria including test times are usually established on the basis of an evaluation of the dissolution profile data. In the opinion of the DB II, a release specification of (b) (4)% at 24 hr adequately captures the terminal release profile of the test product and ensures better quality control against any possible overage in the future test product batches. The above

¹ ANDA 204403 – DARRTS: REV-BIOEQ-02(Dissolution Review) – 3/23/2013

² ANDA 204403 – DARRTS: REV-BIOEQ-02(Dissolution Review) – 5/17/2013

³ ANDA 204403 – DARRTS: COR-ANDA-09(Bio Dissolution Deficiencies) – 5/23/2013

mentioned DB recommended release specifications are based on the firm's submitted release data.

The firm will need to provide adequate justification for its proposed release specification of NLT (b) (4) % at the 24-hour time point. Alternatively, the firm may acknowledge the following DB II recommended dissolution method and revised DB II recommended release specifications:

Medium:	0.9% NaCl
Volume:	500 mL
Apparatus:	Modified USP Type VI (Cylinder)
Speed:	50 rpm
Temperature:	32 °C

Specifications:

1 hr:	(b) (4)
2 hr:	(b) (4)
4 hr:	(b) (4)
9 hr:	(b) (4)
24 hr:	(b) (4)

The firm's dissolution testing is incomplete.

2 REVIEW OF SUBMISSION

In the deficiency letter of May 23, 2013 (ANDA 204403 – DARRTS: COR-ANDA-09(Bio Dissolution Deficiencies)) the firm was informed of the following deficiency.

DB deficiency:

You have conducted acceptable dissolution testing; however, your proposed dissolution specifications are not acceptable. Based on the submitted data, the DBII recommends the following dissolution method and specifications:

*Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C*

Specifications for all strengths (4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr):

*1 hr: (b) (4)
2 hr: (b) (4)
4 hr: (b) (4)
9 hr: (b) (4)
24 hr: (b) (4)*

Please acknowledge the above dissolution method and specifications.

Firm's response:

Alvogen acknowledges and accepts the Division of Bioequivalence II (DBII) request to adopt the FDA recommended dissolution method in replacement of the dissolution method submitted in the original ANDA (as listed in Table 1).

Table 1: Comparison of Current Method and FDA Recommended Method for Dissolution

Setting	Current Method	Recommended Method
Apparatus	(b) (4)	Modified Rotating Cylinder, Apparatus VI
Medium	(b) (4)	0.9% NaCl
Volume	(b) (4)	500 mL
Speed	(b) (4)	50 rpm
Temperature	(b) (4)	32 °C
Sampling	(b) (4)	1 hr, 2 hr, 4 hr, 9 hr, 24 hr

Regarding the FDA proposed specification the applicant proposes the following adjustments in Table 2:

Table 2: Specification for Dissolution Test

Setting	FDA Recommended Specifications	Alvogen Proposed Specifications
1 hr	(b) (4)	(b) (4)
2 hr		
4 hr		
9 hr		
24 hr		

Alvogen's proposed specification is provided in Table 2. It is proposed to slightly shift the specification for the 4 hr sampling point to (b) (4)%. For the 24 hr time point, Alvogen proposes to specify the lower limit (not less than, NLT) and set this limit to (b) (4)%. The specification limit of NLT (b) (4)% is proposed based on the specification criteria for assay of the drug product (b) (4)% of labeled content) and uniformity of dosage units specification limit, which allows for individual patches to be within (b) (4) % of label claim.

Referring to USP 35 Chapter <1092>, Section *Acceptance Criteria*, allowance needs to be made for assay and content uniformity ranges, when establishing the specification. Therefore, the specification of NLT (b) (4)% for the 24 hr time point is considered an appropriate control for the quality of the drug product.

Additionally please note in conjunction with the proposed method referenced above in Table 1; Alvogen will utilize the Acceptance Table 1 criteria delineated in USP General Chapter <724> Drug Release as presented below in Table 3.

Table 3. Acceptance Table 1 - USP General Chapter <724> Drug Release

Level	Number Tested	Criteria
L1	6	No individual value lies outside the stated range
L2	6	The average value of the 12 units (L1 + L2) lies within the stated range. No individual value is outside the stated range by more than 10% of the average of the stated range.
L3	12	The average value of 24 units (L1 + L2 + L3) lies within the stated range. Not more than 2 of the 24 units are outside the stated range by more than 10% of the average of the stated range; and none of the units is outside the stated range by more than 20% of the average of the stated range

Reviewer's Comment:

The DB II acknowledges the firm's request for changing the DB recommended release specification at the 4-hour time point from (b) (4)% to (b) (4)%. The DB II finds a specification of (b) (4)% at the 4-hour time point acceptable. However, the DB II does

not find the firm's rationale for changing the DB II proposed specification of (b) (4) to NLT (b) (4) % at the 24-hour time point adequate.

The reviewer acknowledges the firm's argument that USP Chapter 1092 states that allowance needs to be made for assay and content uniformity ranges. However, it should be noted that USP Chapter 1092 also states the following:

“Acceptance criteria including test times are usually established on the basis of an evaluation of the dissolution profile data. Acceptance criteria should be consistent with historical data, and there is an expectation that acceptable batches (e.g., no significant differences in in vivo performance, composition, or manufacturing procedure) will have results that fall within the acceptance criteria.”

Therefore, based on the submitted data, the DB II has recommended a specification of (b) (4) % at the 24-hour time point for all strengths of the test product.

The firm will be asked to provide further justification for its proposed specification of NLT (b) (4) % at the 24-hour time point. Alternatively, the firm may acknowledge the following DB II recommended dissolution method and revised DB II recommended release specifications:

Medium:	0.9% NaCl
Volume:	500 mL
Apparatus:	Modified USP Type VI (Cylinder)
Speed:	50 rpm
Temperature:	32 °C

Specifications:

1 hr:	(b) (4)
2 hr:	(b) (4)
4 hr:	(b) (4)
9 hr:	(b) (4)
24 hr:	(b) (4)

3 DEFICIENCY COMMENTS

The DB II finds the firm's proposed release specification of (b) (4)% at the 4-hour time point acceptable. However, although allowances for assay and content uniformity ranges are taken into consideration, per USP Chapter 1092, acceptance criteria including test times are usually established on the basis of an evaluation of the dissolution profile data. The DB II has recommended a release specification of (b) (4)% at the 24-hour time point based on the submitted data. In the opinion of the DB II, a release specification of (b) (4)% at 24 hr adequately captures the terminal release profile of the test product and ensures better quality control against any possible overage in the future test product batches. The firm's rationale for changing the specification at the 24-hour time point is inadequate. The firm will need to provide adequate justification for a release specification of NLT (b) (4)% at the 24-hour time point. Alternatively, the firm may acknowledge the following DB II recommended dissolution method and revised DB II recommended release specifications:

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications:

1 hr: (b) (4)
2 hr: (b) (4)
4 hr: (b) (4)
9 hr: (b) (4)
24 hr: (b) (4)

4 RECOMMENDATIONS

The firm's dissolution testing comparing Rivastigmine Transdermal System 4.6 mg/24hr (lot # C0002AL0AT), 9.5 mg/24hr (lot # C0004AL0AU), and 13.3 mg/24 hr (lot # C0014AL0BC) to Novartis Pharmaceuticals Corporation's Exelon® Patch, 4.6 mg/24hr (lot # 1200 BA), 9.5 mg/24hr (lot # 1401B), and 13.3 mg/24 hr (lot # 2302A BA) is incomplete due to the deficiency listed above.

5 ADDITIONAL ATTACHMENT

None.

BIOEQUIVALENCE DEFICIENCY

ANDA: 204403
APPLICANT: Alvogen Pine Brook, Inc.
DRUG PRODUCT: Rivastigmine Transdermal System; 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr

The Division of Bioequivalence II (DB II) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence study and waiver requests will be conducted later. The following deficiency has been identified:

The DB II finds your proposed release specification of (b) (4) % at the 4-hour time point acceptable. However, your proposed release specification of NLT (b) (4) % at the 24-hour time point is not acceptable. Although allowances for assay and content uniformity ranges are taken into consideration, per USP Chapter <1092>, acceptance criteria including test times are usually established on the basis of an evaluation of the dissolution profile data, as per USP Chapter <1092>. The DB II has recommended a release specification of (b) (4) % at the 24-hour time point based on your submitted data. In the opinion of the DB II, this specification adequately captures the terminal release profile of the test product and ensures better quality control against any possible overage in the future test product batches. Your rationale for changing the specification at the 24-hour time point is inadequate. Please provide adequate justification for your proposed release specification of NLT (b) (4) % at the 24-hour time point. Alternatively, you may acknowledge the following DB II-recommended dissolution method and revised DB II-recommended release specifications:

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications:

1 hr: (b) (4)
2 hr: (b) (4)

4 hr:  (b) (4)
9 hr: 
24 hr: 

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA: 204403; Applicant: Alvogen Pine Brook, Inc.; Drug Product: Rivastigmine
Transdermal System; 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr

Productivity Data
Completed Assignment for 204403 ID: 20529

Reviewer: Raofi, Saeid

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Rivastigmine Transdermal System

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
20529	6/20/2013	Dissolution Data (REGULAR)	Dissolution Amendment	1	1
				Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Dissolution Study	
Dissolution Amendment	1
Dissolution Amendment	0
Total	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SAEID RAOFI
08/28/2013

CHANDRA S CHAURASIA
08/28/2013

Parthapratim CHANDAROY on behalf of ETHAN M STIER
09/13/2013

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	204403
Drug Product Name	Rivastigmine Transdermal System
Strength (s)	4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr
Applicant Name	Alvogen Pine Brook, Inc.
Applicant Address	10 Bloomfield Avenue Building B Pine Brook, NJ 07058
US Agent Name and the mailing address	Jasmine Shah – VP, Regulatory and Medical Affairs
US Agent's Telephone Number	(b) (6)
US Agent's Fax Number	973-201-1086
Original Submission Date(s)	June 12, 2012
Submission Date(s) of Amendment(s) Under Review	April 11, 2013 and May 2, 2013
First Generic	No
Reviewer	Saeid Raofi
Study Number (s)	R10-1307
Study Type (s)	PK study (relative bioavailability and adhesive properties of a transdermal system)
Strength(s)	9.5 mg / 24 Hours Patch
Clinical Site	Cetero Research
Clinical Site Address	4801 Amber Valley Parkway Fargo, ND 58104, USA
Analytical Site	(b) (4)
Analytical Address	
Dissolution Method	Correct
OVERALL REVIEW RESULT	INADEQUATE

Review of 2 Dissolution Amendments

1 EXECUTIVE SUMMARY

This is a review of 2 dissolution amendments dated April 11, 2013 and May 2, 2013.

In the original submission of June 12, 2012 the firm had provided inconsistent information on the regulatory dissolution method used in dissolution summary tables and dissolution data tables on individual units. In the deficiency letter of March 27, 2013¹ the firm was asked to repeat the regulatory dissolution testing using FDA recommended method. In the amendment of April 11, 2013 the firm submitted revised dissolution summary tables and dissolution data tables on individual units clarifying that dissolution testing method used in the original submission is the same as the FDA recommended method.

In the deficiency letter of March 27, 2013 the firm was also asked to provide the rotation speed and dissolution summary tables for the multimedia dissolution testing, specify detection method in dissolution method validation, and provide the certificate of analysis (COA) for the 4.6 mg/24 hr (lot #1200BA), 9.5 mg/24 hr (lot # 1401B) and 13.3 mg/24 hr (lot # 2302A) strengths of the reference product.

In the amendment of April 11, 2013 the firm provided the rotation speed for multimedia dissolution testing, clarified that the detection method in dissolution method validation is UV, and provided the COA for all three strengths of the reference product. However, the firm did not submit dissolution summary tables for multimedia dissolution testing. In a bioequivalence telephone amendment request dated April 30, 2013², the DB II requested that the firm submit these summary tables. The firm submitted the dissolution summary tables for the multimedia dissolution testing in the amendment of May 2, 2013. The test products demonstrate no potential for dose-dumping in pH 1.2 HCl, pH 4.5 acetate, and pH 6.8 phosphate buffers.

The firm has conducted acceptable regulatory dissolution testing using the following FDA recommended dissolution method:

Medium:	0.9% NaCl
Volume:	500 mL
Apparatus:	Modified USP Type VI (Cylinder)
Speed:	50 rpm
Temperature:	32 °C

However, the firm-proposed dissolution specifications are not acceptable. Based on the submitted data the DB II recommends the following dissolution specifications for all strengths of the test product (4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr):

¹ ANDA 204403 – DARRTS: COR-ANDADE-01(Bio Incomplete Deficiencies)

² (ANDA 204403 – DARRTS: COR-ANDAIR-01(Advice/Information Request))

1 hr:  (b) (4)
2 hr: 
4 hr: 
9 hr: 
24 hr: 

The firm will be asked to acknowledge the above dissolution method and specifications.

The firms dissolution testing is incomplete.

2 REVIEW OF SUBMISSION

In the deficiency letter of March 27, 2013 (ANDA 204403 – DARRTS: COR-ANDA-01(Bio Incomplete Deficiencies)) the firm was informed of 4 deficiencies. These deficiencies, the firm's response, and reviewer comments are listed below.

DB deficiency 1:

In the cover letter of the amendment dated January 22, 2013, you have proposed to use the FDA-recommended dissolution apparatus, Modified USP Apparatus Type VI (Cylinder), for all 3 strengths of the test product. However, the dissolution testing methods reported in the dissolution summary table submitted on January 22, 2013 and in the dissolution data tables on the individual dosage units (submitted on June 12, 2012 for the 4.6 mg/24 hr and 9.5 mg/24 hr strengths, and on January 22, 2013 for the 13.3 mg/24 hr strength) are different, and neither one of these methods matches the FDA-recommended method. Additionally, you have not specified the rotation speed. Please also note that the data provided on the 4.6 mg/24 hr and 9.5 mg/24 hr strengths in the dissolution summary table (in the submission of January 22, 2013) are the data from dissolution testing conducted using your own proposed method submission dated June 12, 2012 (b) (4). Please conduct dissolution testing on 12 individual units each of the test and reference products for all 3 strengths (4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr) using the following FDA-recommended dissolution method:

Medium:	0.9% NaCl
Volume:	500 mL
Apparatus:	Modified USP Type VI (Cylinder)
Speed:	50 rpm
Temperature:	32 °C

Please submit data on individual units, means, range and % CV including f2 similarity values and dissolution plots. Please clearly state the dissolution testing method used in all dissolution summary tables and dissolution data tables on individual dosage units. Additionally, you may refer to the Agency's dissolution guidance on Rivastigmine Transdermal System at <http://www.accessdata.fda.gov/scripts/cder/dissolutio>

Firm's response:

The comparative and multimedia dissolution tables were provided in the Original ANDA (Sequence 0000) and CMC Amendment (0003). The comparative dissolution testing was performed on twelve individual units of the test and reference products for all three dosage strengths (4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr) using the FDA recommended dissolution method.

The dissolution tables were updated to more clearly provide data on individual units, mean values, ranges (given as "minimum" and "maximum"), % CV (RSD [%]) and

the f2 similarity factors as well as the dissolution plots. The revised tables are provided in **Module 2.7.1.2.**

Additionally the eCTD Summary Table 5, "Summary of In-Vitro Dissolution Studies" have been updated based on the dissolution results for the FDA recommended dissolution media testing and are also provided in **Module 2.7.1.2.**

The multimedia dissolution comparison tables were also revised into the updated dissolution table format and are in **Module 2.7.1.2.** The multimedia dissolution for 4.6 mg/24 hr and 9.5 mg/24 hr is provided utilizing both the (b) (4) and (b) (4). For Rivastigmine Transdermal System 13.3 mg/24 hr the multimedia dissolution comparison was only performed utilizing the (b) (4). Due to the size of Rivastigmine Transdermal System, 13.3 mg/24 hr it was not feasible to execute testing utilizing the (b) (4).

The multimedia dissolution tables clearly describe the batch/strength, apparatus, medium, volume and rotation speed. The tables provide the data on individual units, mean values, ranges (given as "minimum" and "maximum"), % CV (RSD [%]) and the f2 similarity factors as well as the dissolution plot.

Lastly, comparative dissolution between the 3 proposed dosage strengths for Rivastigmine Transdermal System (4.6 mg/24hr, 9.5 mg/24hr and 13.3124 hr) is provided in **Module 2.7.1.2.** utilizing the FDA recommended dissolution method/media. The results of this comparison provide additional evidence of a highly similar release profile of Alvogen's proposed Rivastigmine Transdermal System. Independent of the patch area, all the dosage strengths exhibit a similar in-vitro release profile as indicated by F2 value > 70.

Additionally as discussed in the product development report in **Module 3.2.P.2. (Sequence 0000)** an in-vitro, in-vivo correlation (IVIVC) was not able to be established for this product and as is the case with many transdermal patch products. The dissolution (in-vitro release) test is performed to insure consistent lot-to-lot drug release.

Dissolution Conditions		Apparatus:	Modified USP Type VI (Rotating Cylinder)									
		Medium:	0.9% NaCl at 32°C									
		Volume:	500 mL									
		Temperature:	32 ± 0.5°C									
		Rotation Speed	50 RPM									
Firm's Proposed Specifications		Level 1:	6 patches are tested and each patch complies with the specification:									
		1 h:	(b) (4)									
		4 h:	(b) (4)									
		24 h:	(b) (4)									
		Level 2:	6 additional patches are tested and the mean of 12 patches (Level 1 + Level 2) must comply with the Level 1 specification above and no patch is allowed to be outside of the following specification:									
		1 h:	(b) (4)									
		4 h:	(b) (4)									
		24 h:	(b) (4)									
		Level 3:	12 additional patches are tested and the mean of 24 patches (Level 1 + Level 2 + Level 3) must comply with the above mentioned Level 1 specification. Maximum of two patches are allowed to be outside of the following specification:									
		1 h:	(b) (4)									
		4 h:	(b) (4)									
		24 h:	(b) (4)									
		and no patch is allowed to be outside of the following specification:										
		1 h:	(b) (4)									
		4 h:	(b) (4)									
		24 h:	(b) (4)									
Dissolution Testing Site (Name, Address)		(b) (4)										
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (hours)							Study Report Location
					0	1	2	4	7	9	12	

C10-1870	07/22/2011 – 8/8/2011	Rivastigmine Transdermal System / Batch No. C0002AL0AT (Manufactured – 06/27/2011)	4.6 mg/24 hr	12	Mean	0	23.53	38.01	57.69	73.72	79.59	84.64	90.60	Module 1.12.12
		Exelon Patch (Batch No. 1200 BA) Expiration Date: Oct 2012	4.6 mg/24 hr	12	Range	(b) (4)								
					%CV	-	3.09	1.72	1.68	1.82	2.07	2.03	1.58	
					Mean	0	40.10	56.34	69.83	78.10	81.04	84.06	89.64	
					Range	(b) (4)								
		%CV	-	0.69	0.80	0.86	0.90	0.92	0.98	1.05				
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes or hours)								Study Report Location	
C10-1870	07/18/2011 – 8/12/2011	Rivastigmine Transdermal System / Batch No. C0004AL0AU (Manufactured – 06/27/2011)	9.5 mg/24 hr	12	Mean	0	23.04	37.85	58.20	74.89	81.04	86.43	92.41	Module 1.12.12
		Exelon Patch (Batch No. 1401B) Expiration Date: Jan 2013	9.5 mg/24 hr	12	Range	(b) (4)								
					%CV	-	1.98	1.33	1.24	1.77	2.05	2.24	2.78	
					Mean	0	40.67	56.41	68.42	75.56	78.44	81.53	87.23	
					Range	(b) (4)								
		%CV	-	1.00	0.75	0.69	0.59	0.58	0.53	0.73				
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes or hours)								Study Report Location	
	11/20/2012	Rivastigmine	13.3	12	Mean	0	22.29	37.79	59.74	77.86	84.41	90.02	95.84	Module

	Transdermal System / Batch No. C0014AL0BC (Manufactured – 10/08/2012)	mg/24 hr		Range	(b) (4) 2.7.1							
				%CV	-	1.30	0.94	0.66	1.04	1.38	1.73	1.65
				Mean	0	39.75	56.10	68.46	75.33	78.07	81.09	87.04
	Exelon Patch (Batch No. 2302A BA) Expiration Date: April 2014	13.3 mg/24 hr	12	Range	(b) (4)							
				%CV	-	1.85	0.98	0.93	0.85	0.97	0.95	0.81

Test results for comparative dissolution testing of (b) (4) Rivastigmine patches 4.6 mg/ 24h versus Exelon® patches 0.9% NaCl

Method	Performance according to trial protocol issued 23.01.2012; Chromatographic analysis according to Testing Standard "Release and Shelf life Rivastigmine 4.6 cm2, 9.2 cm2 and 13.8 cm2 Alvogen" chapter 5 "In vitro Drug Release" dated 23.10.2012

Trial:	C0002AL0AT, NaCl, Rotating Cylinder	Patch Area [cm²]:	4.6
Apparatus:	Modified USP Type VI (Cylinder)	API Amount [%]:	(b) (4)
Medium:	0.9 % NaCl		
Volume [ml]:	500.0		
Rotation speed [rpm]:	50		

time [h]	0	1	2	4	7	9	12	24
	Amount released [%]							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0.00	23.53	38.01	57.69	73.72	79.59	84.64	90.60
Minimum	(b) (4)							
Maximum	(b) (4)							
SD	0.00	0.73	0.65	0.97	1.34	1.65	1.72	1.43
RSD [%]	-	3.09	1.72	1.68	1.82	2.07	2.03	1.58

Trial:	Exelon #1200BA, NaCl, Rotating Cylinder	Patch Area [cm²]:	5
Apparatus:	Modified USP Type VI (Cylinder)	API Amount [%]:	(b) (4)
Medium:	0.9 % NaCl		
Volume [ml]:	500.0		
Rotation speed [rpm]:	50		

time [h]	0	1	2	4	7	9	12	24
	Amount released [%]							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0.00	40.10	56.34	69.83	78.10	81.04	84.06	89.64
Minimum	(b) (4)							
Maximum	(b) (4)							
SD	0.00	0.28	0.45	0.60	0.71	0.75	0.82	0.94
RSD [%]	-	0.69	0.80	0.86	0.90	0.92	0.98	1.05

Test results for comparative dissolution testing of (b) (4) Rivastigmine patches 9.5 mg/ 24h versus Exelon® patches 0.9 % NaCl

Method Performance according to trial protocol issued 23.01.2012; Chromatographic analysis according to Testing Standard "Release and Shelf life Rivastigmine 4.6 cm2, 9.2 cm2 and 13.8 cm2 AlvoGen" chapter 5 "In vitro Drug Release" dated 23.10.2012

Trial: C0004AL0AU NaCl Rotating Cylinder **Patch Area [cm²]:** 9.2
Apparatus: Modified USP Type VI (Cylinder) **API Amount [%]:** (b) (4)
Medium: 0.9% NaCl
Volume [ml]: 500.0
Rotation speed [rpm]: 50

time [h]	0	1	2	4	7	9	12	24
	Amount released [%]							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0.00	23.04	37.85	58.20	74.89	81.04	86.43	92.41
Minimum	(b) (4)							
Maximum	(b) (4)							
SD	0.00	0.46	0.50	0.72	1.33	1.66	1.93	2.57
RSD [%]	-	1.98	1.33	1.24	1.77	2.05	2.24	2.78

Trial: Exelon #1401B NaCl Rotating Cylinder **Patch Area [cm²]:** 10
Apparatus: Modified USP Type VI (Cylinder) **API Amount [%]:** (b) (4)
Medium: 0.9% NaCl
Volume [ml]: 500.0
Rotation speed [rpm]: 50

time [h]	0	1	2	4	7	9	12	24
	Amount released [%]							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0.00	40.67	56.41	68.42	75.56	78.44	81.53	87.23
Minimum	(b) (4)							
Maximum	(b) (4)							
SD	0.00	0.41	0.42	0.47	0.44	0.45	0.43	0.64
RSD [%]	-	1.00	0.75	0.69	0.59	0.58	0.53	0.73

Test results for comparative dissolution testing of (b) (4) Rivastigmine patches 13.3 mg/ 24h versus Exelon® patches 0.9% NaCl

Method Performance according to trial protocol dated 26.10.2012; Chromatographic analysis according to Testing Standard "Release and Shelf life Rivastigmine 4.6 cm2, 9.2 cm2 and 13.8 cm2 Alvogen" chapter 5 "In vitro Drug Release" dated 23.10.2012

Trial: C0014AL0BC, NaCl, Rotating Cylinder Patch Area [cm²]: 13.8
 Apparatus: Modified USP Type VI (Cylinder) API Amount [%]: (b) (4)
 Medium: 0.9% NaCl
 Volume [ml]: 500.0
 Rotation speed [rpm]: 50

time [h]	0	1	2	4	7	9	12	24
	Amount released [%]							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0.00	22.29	37.79	59.74	77.86	84.41	90.02	95.84
Minimum	(b) (4)							
Maximum	(b) (4)							
SD	0.00	0.29	0.36	0.39	0.81	1.16	1.55	1.58
RSD [%]	-	1.30	0.94	0.66	1.04	1.38	1.73	1.65

Trial: Exelon #2302A, NaCl, Rotating Cylinder Patch Area [cm²]: 15
 Apparatus: Modified USP Type VI (Cylinder) API Amount [%]: (b) (4)
 Medium: 0.9% NaCl
 Volume [ml]: 500.0
 Rotation speed [rpm]: 50

time [h]	0	1	2	4	7	9	12	24
	Amount released [%]							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0.00	39.75	56.10	68.46	75.33	78.07	81.09	87.04
Minimum	(b) (4)							
Maximum	(b) (4)							
SD	0.00	0.73	0.55	0.64	0.64	0.76	0.77	0.71
RSD [%]	-	1.85	0.98	0.93	0.85	0.97	0.95	0.81

Reviewer's Comment:

In its response the firm has clarified that it had submitted the results of regulatory dissolution testing conducted using the FDA recommended method on the 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr strengths of the test and reference products. The firm has submitted revised dissolution summary tables and dissolution data tables on individual dosage units in the current amendment. The dissolution method information provided in these tables are consistent now and both the summary table and individual unit data tables show that the firm has conducted the regulatory dissolution testing using the following FDA recommended method:

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

The firm has conducted acceptable dissolution testing; however, the firm proposed dissolution specifications (please see dissolution summary table above) are not acceptable. Based on the submitted data and to be consistent with time points recommended for 1 previously reviewed application on this product (please see additional attachment), the DB II recommends the following dissolution specifications:

1 hr: (b) (4)
2 hr: (b) (4)
4 hr: (b) (4)
9 hr: (b) (4)
24 hr: (b) (4)

The firm will be asked to acknowledge the above DB II recommended dissolution method and specifications.

DBE deficiency 2:

Please specify the rotation speed and submit dissolution summary tables for all multimedia dissolution testing.

Firm's response:

The multimedia dissolution tables have been revised to include rotation speed (and other attributes as discussed in question I). For the dissolution comparison utilizing the (b) (4) rotation speed was utilized. For dissolution performed utilizing the (b) (4)

RPM was utilized. The updated multimedia dissolution tables are provided in Module 2.7.1.2

Reviewer's Comment:

The firm submitted revised multimedia dissolution testing data tables that include the requested information on rotation speed, but did not submit multimedia dissolution summary tables, and was requested to submit this information through a bioequivalence telephone amendment request dated April 30, 2013 (ANDA 204403 – DARRTS: COR-ANDAIR-01(Advice/Information Request)). In an amendment dated May 2, 2013, the firm provided the dissolution summary tables. It is noted that the firm has conducted multimedia dissolution testing in pH 1.2 HCl, pH 4.5 acetate, and pH 6.8 phosphate (b) (4) rpm for 4.6 mg/24hr and 9.5 mg/24hr patches, and 500 mL of medium and modified USP Apparatus Type VI at 50 rpm for 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr patches.

Multi media dissolution testing using

[Redacted]

(b) (4)

rpm (4.6 mg/24hr, 9.5

[Redacted]

(b) (4)

Multimedia dissolution testing using 500 mL medium and modified USP Apparatus Type VI at 50 rpm (4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr patches)

Dissolution Conditions	Apparatus:	Modified USP Type VI (Rotating Cylinder)
	Medium:	Hydrochloric acid buffer pH 1.2
	Volume:	500 mL
	Temperature:	32 ± 0.5°C
	Rotation Speed	50 RPM
Firm's Proposed Specifications	Level 1: 6 patches are tested and each patch complies with the specification:	
	1 h:	(b) (4)
	4 h:	
	24 h:	
Level 2: 6 additional patches are tested and the mean of 12 patches (Level 1 + Level 2) must comply with the Level 1 specification above and no patch is allowed to be outside of the following specification:		
1 h:	(b) (4)	
4 h:		
24 h:		
Level 3: 12 additional patches are tested and the mean of 24 patches (Level 1 + Level 2 + Level 3) must comply with the above mentioned Level 1 specification. Maximum of two patches are allowed to be outside of the following specification:		
1 h:	(b) (4)	
4 h:		
24 h:		
and no patch is allowed to be outside of the following specification:		
1 h:	(b) (4)	
4 h:		
24 h:		

(b) (4)

Dissolution Testing Site (Name, Address)														
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (hours)								Study Report Location	
					0	1	2	4	7	9	12	24		
C10-1870	07/22/2011 – 8/8/2011	Rivastigmine Transdermal System / Batch No. C0002AL0AT (Manufactured – 06/27/2011)	4.6 mg/24 hr	12	Mean	0	27.14	42.79	62.54	77.23	82.60	87.07	92.47	Module 2.7.1
					Range	(b) (4)								
					%CV	-	3.22	2.25	1.40	1.07	1.06	1.05	1.59.	
		Exelon Patch (Batch No. 1200 BA) Expiration Date: Oct 2012	4.6 mg/24 hr	12	Mean	0	47.74	61.87	72.43	78.40	80.50	82.61	86.19	
					Range	(b) (4)								
					%CV	-	1.44	0.92	0.76	0.74	0.73	0.77	0.76	

Dissolution Conditions	Apparatus:	Modified USP Type VI (Rotating Cylinder)
	Medium:	Acetate Buffer pH 4.5
	Volume:	500 mL

	Temperature:	32 ± 0.5°C										
	Rotation Speed	50 RPM										
Firm's Proposed Specifications	Level 1: 6 patches are tested and each patch complies with the specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4)											
	Level 2: 6 additional patches are tested and the mean of 12 patches (Level 1 + Level 2) must comply with the Level 1 specification above and no patch is allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4)											
	Level 3: 12 additional patches are tested and the mean of 24 patches (Level 1 + Level 2 + Level 3) must comply with the above mentioned Level 1 specification. Maximum of two patches are allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4) and no patch is allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4)											
Dissolution Testing Site (Name, Address)	(b) (4)											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (hours)							Study Report Location
					0	1	2	4	7	9	12	

		(Reference – Expiration Date)															
C10-1870	07/22/2011 – 8/8/2011	Rivastigmine Transdermal System / Batch No. C0002AL0AT (Manufactured – 06/27/2011)	4.6 mg/24 hr	12	Mean	0	24.99	40.09	60.14	75.38	80.54	84.96	90.72	Module 2.7.1			
					Range	(b) (4)											
					%CV	-	3.64	2.43	1.28	0.80	0.74	0.96	1.56				
		Exelon Patch (Batch No. 1200 BA) Expiration Date: Oct 2012	4.6 mg/24 hr	12	Mean	0	43.83	56.83	67.03	72.98	85.21	77.56	83.01				
					Range	(b) (4)											
					%CV	-	1.28	1.31	1.12	1.18	1.31	1.27	1.24				

Dissolution Conditions	Apparatus:	Modified USP Type VI (Rotating Cylinder)
	Medium:	Phosphate Buffer pH 6.8
	Volume:	500 mL
	Temperature:	32 ± 0.5°C
	Rotation Speed	50 RPM

Firm's Proposed Specifications	Level 1: 6 patches are tested and each patch complies with the specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4) Level 2: 6 additional patches are tested and the mean of 12 patches (Level 1 + Level 2) must comply with the Level 1 specification above and no patch is allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4) Level 3: 12 additional patches are tested and the mean of 24 patches (Level 1 + Level 2 + Level 3) must comply with the above mentioned Level 1 specification. Maximum of two patches are allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4) and no patch is allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4)											
	Dissolution Testing Site (Name, Address)											
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (hours)							Study Report Location
					0	1	2	4	7	9	12	

C10-1870	07/22/2011 – 8/8/2011	Rivastigmine Transdermal System / Batch No. C0002AL0AT (Manufactured – 06/27/2011)	4.6 mg/24 hr	12	Mean	0	23.53	38.16	57.87	73.71	79.61	84.49	90.92	Module 2.7.1		
					Range	(b) (4)										
					%CV	-	4.42	3.35	2.16	1.71	1.61	1.72	1.93			
		Mean	0	46.52	60.52	71.05	77.11	79.62	81.89	86.56	(b) (4)					
		Range														
		%CV	-	1.20	0.84	0.82	1.04	1.09	1.07	1.25						

Dissolution Conditions	Apparatus:	Modified USP Type VI (Rotating Cylinder)
	Medium:	Hydrochloric Acid buffer pH 1.2
	Volume:	500 mL
	Temperature:	32 ± 0.5°C
	Rotation Speed	50 RPM
Firm's Proposed Specifications	Level 1: 6 patches are tested and each patch complies with the specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4)	
	Level 2:	

6 additional patches are tested and the mean of 12 patches (Level 1 + Level 2) must comply with the Level 1 specification above and no patch is allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4) Level 3: 12 additional patches are tested and the mean of 24 patches (Level 1 + Level 2 + Level 3) must comply with the above mentioned Level 1 specification. Maximum of two patches are allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4) and no patch is allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4)														
Dissolution Testing Site (Name, Address)		(b) (4)												
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes or hours)								Study Report Location	
					0	1	2	4	7	9	12	24		
C10-1870	07/18/2011 – 8/12/2011	Rivastigmine Transdermal System / Batch No. C0004AL0AU (Manufactured – 06/27/2011)	9.5 mg/24 hr	12	Mean	0	27.46	43.56	64.78	80.01	85.60	90.22	95.73	Module 2.7.1
					Range	(b) (4)								
					%CV	-	4.74	4.52	3.89	3.67	3.68	3.53	3.69	

		Exelon Patch (Batch No. 1401B) Expiration Date: Jan 2013	9.5 mg/24 hr	12	Mean	0	47.9 6	62.50	73.2 0	79.5 2	87.5 7	83.6 3	87.33 (b) (4)
					Range								
					%CV	-	0.55	0.46	0.50	1.05	0.70	1.00	1.05

Dissolution Conditions	Apparatus:	Modified USP Type VI (Rotating Cylinder)
	Medium:	Acetate Buffer pH 4.5
	Volume:	500 mL
	Temperature:	32 ± 0.5°C
	Rotation Speed	50 RPM
Firm's Proposed Specifications	Level 1:	6 patches are tested and each patch complies with the specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4)
	Level 2:	6 additional patches are tested and the mean of 12 patches (Level 1 + Level 2) must comply with the Level 1 specification above and no patch is allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4)
	Level 3:	12 additional patches are tested and the mean of 24 patches (Level 1 + Level 2 + Level 3) must comply with the above mentioned Level 1 specification. Maximum of two patches are allowed to be outside of the following specification:

		1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4) and no patch is allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4)												
Dissolution Testing Site (Name, Address)		(b) (4)												
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes or hours)								Study Report Location	
					0	1	2	4	7	9	12	24		
C10-1870	07/18/2011 – 8/12/2011	Rivastigmine Transdermal System / Batch No. C0004AL0AU (Manufactured – 06/27/2011)	9.5 mg/24 hr	12	Mean	0	26.19	41.76	62.07	77.26	82.32	86.51	91.61	Module 2.7.1
					Range	(b) (4)								
					%CV	-	3.97	2.91	2.00	2.03	2.24	2.28	2.60	
		Exelon Patch (Batch No. 1401B) Expiration Date: Jan 2013	9.5 mg/24 hr	12	Mean	0	44.0	58.59	69.55	75.96	78.51	81.14	87.34	
					Range	(b) (4)								
					%CV	-	1.54	0.63	0.60	0.79	0.87	0.79	1.00	

Dissolution Conditions	Apparatus:	Modified USP Type VI (Rotating Cylinder)
	Medium:	Phosphate Buffer 6.8
	Volume:	500 mL
	Temperature:	32 ± 0.5°C
	Rotation Speed	50 RPM
Firm's Proposed Specifications	Level 1: 6 patches are tested and each patch complies with the specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4) Level 2: 6 additional patches are tested and the mean of 12 patches (Level 1 + Level 2) must comply with the Level 1 specification above and no patch is allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4) Level 3: 12 additional patches are tested and the mean of 24 patches (Level 1 + Level 2 + Level 3) must comply with the above mentioned Level 1 specification. Maximum of two patches are allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4) and no patch is allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4)	

Dissolution Testing Site (Name, Address)														
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes or hours)								Study Report Location	
					0	1	2	4	7	9	12	24		
C10-1870	07/18/2011 – 8/12/2011	Rivastigmine Transdermal System / Batch No. C0004AL0AU (Manufactured – 06/27/2011)	9.5 mg/24 hr	12	Mean	0	25.14	40.34	60.66	76.04	81.51	86.13	91.43	Module 2.7.1
					Range	(b) (4)								
					%CV	-	5.0	3.52	2.12	0.77	0.62	0.60	0.98	
		Exelon Patch (Batch No. 1401B) Expiration Date: Jan 2013	9.5 mg/24 hr	12	Mean	0	48.56	62.99	73.69	79.89	82.25	84.56	89.17	
					Range	(b) (4)								
					%CV	-	0.47	0.26	0.27	0.25	0.30	0.33	0.49	

Dissolution Conditions	Apparatus:	Modified USP Type VI (Rotating Cylinder)
	Medium:	Hydrochloric Acid buffer pH 1.2
	Volume:	500 mL
	Temperature:	32 ± 0.5°C

		Rotation Speed	50 RPM										
Firm's Proposed Specifications	Level 1: 6 patches are tested and each patch complies with the specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4) Level 2: 6 additional patches are tested and the mean of 12 patches (Level 1 + Level 2) must comply with the Level 1 specification above and no patch is allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4) Level 3: 12 additional patches are tested and the mean of 24 patches (Level 1 + Level 2 + Level 3) must comply with the above mentioned Level 1 specification. Maximum of two patches are allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4) and no patch is allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4)												
	Dissolution Testing Site (Name, Address)	(b) (4)											
Study Ref	Testing Date	Product ID \ Batch No. (Test - Manufacture)	Dosage Strength	No. of Dosage	Collection Times (minutes or hours)								Study Report
					0	1	2	4	7	9	12	24	

No.		Date) (Reference – Expiration Date)	& Form	Units											Location	
	11/20/2012	Rivastigmine Transdermal System / Batch No. C0014AL0BC (Manufactured – 10/08/2012)	13.3 mg/24 hr	12	Mean	0	27.5 9	44.66	66.8 5	83.5 6	89.0 3	91.4 3	97.59	Module 2.7.1		
					Range	(b) (4)										
					%CV	-	2.84	2.55	1.98	1.35	1.36	1.02	1.18			
		Mean	0	48.3 7	43.10	73.4 0	79.3 1	81.3 6	83.4 2	87.19	(b) (4)					
		Range														
		%CV	-	1.99	0.91	0.50	0.35	0.30	0.41	0.52						

Dissolution Conditions	Apparatus:	Modified USP Type VI (Rotating Cylinder)
	Medium:	Acetate Buffer pH 4.5
	Volume:	500 mL
	Temperature:	32 ± 0.5°C
	Rotation Speed	50 RPM
Firm's Proposed Specifications	Level 1: 6 patches are tested and each patch complies with the specification: 1 h: (b) (4) 4 h: 24 h:	

Level 2:

6 additional patches are tested and the mean of 12 patches (Level 1 + Level 2) must comply with the Level 1 specification above and no patch is allowed to be outside of the following specification:

1 h: (b) (4)
 4 h: (b) (4)
 24 h: (b) (4)

Level 3:

12 additional patches are tested and the mean of 24 patches (Level 1 + Level 2 + Level 3) must comply with the above mentioned Level 1 specification. Maximum of two patches are allowed to be outside of the following specification:

1 h: (b) (4)
 4 h: (b) (4)
 24 h: (b) (4)

and no patch is allowed to be outside of the following specification:

1 h: (b) (4)
 4 h: (b) (4)
 24 h: (b) (4)

Dissolution Testing Site (Name, Address) (b) (4)

Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)								Study Report Location
						0	1	2	4	7	9	12	24	
	11/20/2012	Rivastigmine Transdermal System /	13.3 mg/24 hr	12	Mean	0	25.0 2	42.25	65.3 7	82.0 4	87.2 7	90.2 2	94.04	Module 2.7.1

		Batch No. C0014AL0BC (Manufactured – 10/08/2012)			Range	(b) (4)							
					%CV	-	1.94	1.53	1.29	0.66	0.90	0.71	0.82
		Exelon Patch (Batch No. 2302A BA) Expiration Date: April 2014	13.3 mg/24 hr	12	Mean	0	42.4 3	55.79	66.4 2	72.5 4	74.7 2	77.1 7	82.64
					Range	(b) (4)							
					%CV	-	0.71	0.46	0.34	0.46	0.48	0.49	0.48



(b) (4)

* Reviewer's Note: For this strength the firm has done dissolution testing in the pH 6.8 Phosphate Buffer (please see the next table); however, the firm additionally reported results of dissolution testing in pH (b) (4) Phosphate Buffer.

Dissolution Conditions	Apparatus:	Modified USP Type VI (Rotating Cylinder)
	Medium:	Phosphate Buffer pH 6.8
	Volume:	500 mL
	Temperature:	32 ± 0.5°C
	Rotation Speed	50 RPM
Firm's Proposed Specifications	Level 1: 6 patches are tested and each patch complies with the specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4)	
	Level 2: 6 additional patches are tested and the mean of 12 patches (Level 1 + Level 2) must comply with the Level 1 specification above and no patch is allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4)	

Level 3: 12 additional patches are tested and the mean of 24 patches (Level 1 + Level 2 + Level 3) must comply with the above mentioned Level 1 specification. Maximum of two patches are allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4) and no patch is allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4)														
Dissolution Testing Site (Name, Address)		(b) (4)												
Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes or hours)								Study Report Location
						0	1	2	4	7	9	12	24	
	11/20/2012	Rivastigmine Transdermal System / Batch No. C0014AL0BC (Manufactured - 10/08/2012)	13.3 mg/24 hr	12	Mean	0	25.2 2	41.56	63.7 9	80.8 4	86.6 7	91.2 7	95.58	Module 2.7.1
					Range	(b) (4)								
					%CV	-	2.67	1.73	1.29	1.04	1.15	1.17	1.48	
		Exelon Patch (Batch No. 2302A BA) Expiration Date: April	13.3 mg/24 hr	12	Mean	0	48.4 8	62.76	73.1 6	79.0 6	81.2 7	83.4 2	87.78	
					Range	(b) (4)								

		2014				(b) (4)							
					%CV	-	1.00	0.70	0.44	0.40	0.37	0.38	0.49

Reviewer comments

The test products demonstrate no potential for dose-dumping under multi-media pH, 1.2 HCl, pH 4.5 acetate, and pH 6.8 phosphate buffers conditions.

DBE deficiency 3:

The dissolution method validation report does not specify the detection method. Please specify the detection method.

Firm's response:

The analysis of the dissolution samples is performed with a reversed phase chromatography system using UV detection at 210 nm. The validation of the dissolution method was conducted based on the analytical procedure, "Testing Standard: Release and Shelf life Rivastigmine 4.6 cm², 9.2 cm² and 13.8 cm²", chapter 5 "In-vitro drug release", which is provided in Sequence 0003, Module 3.2.P.5.2.

The testing standard contains all analytical methods used for release and shelf life testing of Rivastigmine TDS. For each analytical method the corresponding validation report was submitted in Sequence 0000 and Sequence 0003.

Reviewer's Comment:

The firm has provided the requested information. The dissolution method validation is acceptable.

DBE deficiency 4:

Please provide the Certificate of Analysis (COA) for the 4.6 mg/24 hr (lot #1200BA), 9.5 mg/24 hr (lot # 1401B) and 13.3 mg/24 hr (lot # 2302A) strengths of the reference product.

Firm's response:

The Certificate of Analysis for the reference products (4.6 mg/24 hr (Lot #1200 BA, 9.5 mg/24 hr (lot # 1401 B) and 13.3 mg /24 hr (lot #2302A)) are provided in Module 1.12.12.

Additionally eCTD Summary Table 11 has been updated based on the information from the analysis of the reference products.

Reviewer's Comment:

The firm has provided the requested information.

3 DEFICIENCY COMMENTS

The firm has conducted acceptable dissolution testing; however, the firm proposed dissolution specifications are not acceptable. Based on the submitted data the DB II recommends the following dissolution method and specifications:

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications for all strengths of the test product (4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr):

1 hr:  (b) (4)
2 hr: 
4 hr: 
9 hr: 
24 hr: 

The firm will be asked to acknowledge the above dissolution method and specifications.

4 RECOMMENDATIONS

The firm's dissolution testing comparing Rivastigmine Transdermal System 4.6 mg/24hr (lot # C0002AL0AT), 9.5 mg/24hr (lot # C0004AL0AU), and 13.3 mg/24 hr (lot # C0014AL0BC) comparing them to Novartis Pharmaceuticals Corporation's Exelon[®] Patch, 4.6 mg/24hr (lot # 1200 BA), 9.5 mg/24hr (lot # 1401B), and 13.3 mg/24 hr (lot # 2302A BA) is incomplete pending the firm's acknowledgement of the above FDA recommended dissolution method and specifications.

5 ADDITIONAL ATTACHMENT

 (b) (4)

 (b) (4)

(b) (4)

(b) (4)

BIOEQUIVALENCE DEFICIENCY

ANDA: 204403
APPLICANT: Alvogen Pine Brook, Inc.
DRUG PRODUCT: Rivastigmine Transdermal System; 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr

The Division of Bioequivalence II (DB II) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence study will be conducted later. The following deficiency has been identified:

You have conducted acceptable dissolution testing; however, your proposed dissolution specifications are not acceptable. Based on the submitted data, the DB II recommends the following dissolution method and specifications:

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications for all strengths (4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr):

1 hr:  (b) (4)
2 hr: 
4 hr: 
9 hr: 
24 hr: 

Please acknowledge the above dissolution method and specifications.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

6 PRODUCTIVITY DATA

Completed Assignment for 204403 ID: 19765

Reviewer: Raofi, Saeid

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Rivastigmine Transdermal System

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
19765	4/11/2013	Dissolution Data (REGULAR)	Dissolution Amendment	1	1
19765	5/2/2013	Dissolution Data (REGULAR)	Dissolution Amendment	0	0
				Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Dissolution Study	
Dissolution Amendment	1
Dissolution Amendment	0
Total	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SAEID RAOFI
05/16/2013

CHANDRA S CHAURASIA
05/16/2013

ETHAN M STIER
05/17/2013

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	204403
Drug Product Name	Rivastigmine Transdermal System
Strength (s)	4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr
Applicant Name	Alvogen Pine Brook, Inc.
Applicant Address	10 Bloomfield Avenue Building B Pine Brook, NJ 07058
US Agent Name and the mailing address	Jasmine Shah – VP, Regulatory and Medical Affairs
US Agent’s Telephone Number	(b) (6)
US Agent’s Fax Number	973-201-1086
Original Submission Date(s)	June 12, 2012
Submission Date(s) of Amendment(s) Under Review	January 22, 2013 (Major amendment adding the 13.3 mg/24 hr strength and changing firm proposed dissolution method)
First Generic	No
Reviewer	Saeid Raofi
Study Number (s)	R10-1307
Study Type (s)	PK study (relative bioavailability and adhesive properties of a transdermal system)
Strength(s)	9.5 mg / 24 Hours Patch
Clinical Site	Cetero Research
Clinical Site Address	4801 Amber Valley Parkway Fargo, ND 58104, USA
Analytical Site	(b) (4)
Analytical Address	(b) (4)
Dissolution Method	Correct / Incorrect
OVERALL REVIEW RESULT	INADEQUATE

This submission also includes an Irritation and Sensitization study (study # C10-1870 (S11-0069, R10-1318)). The adhesion component of study R10-1307 and the irritation and sensitization study will be subject to Clinical Division review.

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data submitted in an original submission (4.6 mg/24 hr and 9.5 mg/24 hr) and a major amendment (13.3 mg/24 hr).

There is no USP method for this product but there is an FDA recommended method. In the original submission of June 12, 2012, that included only the 4.6 mg/24 hr and 9.5 mg/24 hr strengths, the firm conducted dissolution testing using its own proposed method (utilizing USP (b) (4) and a second method utilizing the apparatus in the FDA recommended

method (Modified USP Apparatus VI). The firm submitted dissolution data tables on individual dosage units and a dissolution summary table. The data and method information provided in these tables are inconsistent.

In the major amendment of January 22, 2013 the firm added the 13.3 mg/24 hr strength to the application and stated that it proposes to use the FDA recommended method for all three strengths. The firm submitted dissolution data tables on individual units of the 13.3 mg/24 hr strength using the following method:

Apparatus:	(b) (4)
Medium:	NaCl
Volume:	500 mL

However, the submitted dissolution summary table on January 22, 2013 states that dissolution testing was conducted in (b) (4) mL of 0.9% NaCl at 32°C using Modified USP type VI apparatus. It is noted that FDA method recommends 500 mL of 0.9% NaCl at 32°C. The information provided on the dissolution method in the dissolution report and dissolution summary table are inconsistent and neither one of the reported methods used by the firm is identical to the FDA recommended method. Furthermore, the data reported in the dissolution summary table for the 4.6 mg/24 hr and 9.5 mg/24 hr are data from dissolution testing conducted using the firm's own proposed method (USP (b) (4)).

Since this is a modified release drug dosage form the firm has conducted multi media dissolution testing in pH 1.2 HCl Buffer, pH 4.5 Acetate Buffer, and pH 6.8 Phosphate Buffer on all strengths. Additionally the firm conducted dissolution testing on the 13.3 mg strength in pH (b) (4) Phosphate Buffer. However the firm has not submitted dissolution summary tables for multimedia testing and has not specified rotation speed in any of the multimedia dissolution testing.

The dissolution testing is incomplete. The firm should conduct dissolution testing using the following FDA-recommended dissolution method.

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Additionally, the firm should specify rotation speed used in multimedia testing and provide the dissolution summary table for multimedia testing.

The firm should also specify the detection method in dissolution method validation, and provide the COA for all strengths of the reference product.

The DB II will review the BE study and waiver requests at a later date.

Table 1: SUBMISSION CONTENT CHECKLIST

Information		YES	NO	N/A	
Is there an FDA-recommended dissolution method?		☒	☐	☐	
Did the firm use the FDA-recommended dissolution method?*		☐	☒	☐	
Is there a USP dissolution method?		☐	☒	☐	
Did the firm use the USP dissolution method?		☐	☐	☒	
Did the firm use 12 units of both test and reference in dissolution testing		☒	☐	☐	
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)		☐	☒	☐	
Did the firm conduct dissolution testing with its own proposed method		☒	☐	☐	
Is FDA method in the public dissolution database (on the web)		☒	☐	☐	
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
	Fed BE study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
	Other study	BE parameters	☒	☐	☐
		Individual data	☒	☐	☐
Are these datasets appropriately submitted? (e.g., are they blank, readable, duplicated, etc.?)		☒	☐	☐	
Are the DBE Summary Tables present in either PDF and/or MS Word Format?		☒	☐	☐	
If any of the tables are missing or incomplete please indicate that in the comments and request the firm to provide the complete DBE Summary Tables 1-16.					
Is the Long Term Storage Stability (LTSS) sufficient to cover the maximum storage time of the study samples?		☒	☐	☐	
If the LTSS is NOT sufficient please request the firm to provide the necessary data.					

*The provided information is inadequate to make a determination whether the firm used the FDA method or not.

Recommended Dissolution Method:

The FDA recommended method in External dissolution database

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Rivastigmine	Film, Transdermal	Modified USP Type VI (cylinder)	50	0.9 % NaCl at 32° C	500	1, 2, 4, 7, 9 and 12 hours	06/10/2009

Not to be released under FOI

The innovator's application (NDA 22083) included 4 strengths, 4.6 mg/24 hr, 9.5 mg/24 hr, 13.3 mg/ 24 hr, and (b) (4). However, at the time of the posting of the above method only the 4.6 mg/24 hr and 9.5 mg/24 hr strengths of the RLD were approved. The 13.3 mg/24 hr strength was later approved on August 31, 2012. The FDA recommended method shown above is the approved method for all three approved strengths of the RLD (NDA 22083 – DARRTS: REV-QUALITY-03(General Review) – 8/30/2012 and REV-CLINPHARM-01(General Review) -6/15/2007). The (b) (4) has not been approved.

II. Original submission of June 12, 2012

The original submission of June 12, 2012 included the 4.6 mg/24 hr and 9.5 mg/24 hr strengths. In that submission the firm proposed its own dissolution method:

(b) (4)

The firm submitted results of dissolution testing on the 4.6 mg/24 hr and 9.5 mg/24 hr strengths using its own proposed method and the following method:

Apparatus:	Rotating Cylinder
Medium:	NaCl
Volume:	500 mL

The firm has not specified rotation speed in either one of the methods mentioned above.

The firm reported the following method in the dissolution summary table submitted on June 12, 2012:

(b) (4)

It is noted that the apparatus and medium in the last table shown above are the same as the FDA recommended method while the volume is different ((b) (4) vs. 500 mL) and the firm has not specified a rotation speed.

The Quality Overall Summary report (module 2.3.P) and finished product Certificates of Analyses for the 4.6 mg/24 hr and 9.5 mg/24 hr strengths indicate that the dissolution testing will utilized USP (b) (4) but they do not provide any further information on the dissolution method.

Therefore, the firm provided inconsistent information regarding its own proposed method in that submission. The dissolution summary table and data tables on individual dosage units submitted on June 12, 2012 are shown below.

Batch	C0002AL0AT (4.6 mg/24 hr)	Apparatus	(b) (4)
Medium	NaCl	Volume	(b) (4)

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	22	35	54	70	77	81	86
Std. Dev.	0	2	2	3	2	2	2	1

Batch	Exelon #1200BA (4.6 mg/24 hr)	Apparatus	(b) (4)
Medium	NaCl	Volume	(b) (4)

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	44	58	69	75	78	81	85
Std. Dev.	0	0	0	0	1	1	1	1

Batch	C0002AL0AT (4.6 mg/24 hr)	Apparatus	Rotating Cylinder
Medium	NaCl	Volume	500 ml

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	24	38	58	74	80	85	91
Std. Dev.	0	1	1	1	1	2	2	1

Batch	Exelon #1200BA (4.6 mg/24 hr)	Apparatus	Rotating Cylinder
Medium	NaCl	Volume	500 ml

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	40	56	70	78	81	84	90
Std. Dev.	0	0	0	1	1	1	1	1

Batch	C0004AL0AU (9.5 mg/24 hr)	Apparatus	(b) (4)
Medium	NaCl	Volume	(b) (4)

Time [h]	0	1	2	4	7	9	12	24
% Released								
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	18	33	57	73	79	85	91
Std. Dev.	0	5	6	1	3	4	2	2

Batch	Exelon #1401B (9.5 mg/24 hr)	Apparatus	(b) (4)
Medium	NaCl	Volume	(b) (4)

Time [h]	0	1	2	4	7	9	12	24
% Released								
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	45	60	71	78	80	82	87
Std. Dev.	0	0	0	1	1	1	1	1

Batch	C0004AL0AU (9.5 mg/24 hr)	Apparatus	Rotating Cylinder
Medium	NaCl	Volume	500 ml

Time [h]	0	1	2	4	7	9	12	24
% Released								
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	23	38	58	75	81	86	92
Std. Dev.	0	0	1	1	1	2	2	3

Batch	Exelon #1401B (9.5 mg/24 hr)	Apparatus	Rotating Cylinder
Medium	NaCl	Volume	500 ml

Time [h]	0	1	2	4	7	9	12	24
% Released								
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	41	56	68	76	78	82	87
Std. Dev.	0	0	0	0	0	0	0	1

As noted earlier, the reported dissolution method in the dissolution summary table does not match either one of the two methods specified in individual unit data tables. However, the reported data in the dissolution summary report match the reported data in individual unit tables where the dissolution apparatus used is (b) (4)

Since this is a modified release drug product the firm also conducted multimedia dissolution testing.

Batch	C0002AL0AT (4.6 mg/24 hr)	Apparatus	(b) (4)
Medium	pH 1.2 (hydrochloric acid buffer)	Volume	(b) (4)

Time [h]	0	1	2	4	7	9	12	24
% Released								
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	25	40	59	74	79	84	88
Std. Dev.	0	0	0	0	0	1	1	2

Batch	Exelon #1200BA (4.6 mg/24 hr)	Apparatus	(b) (4)
Medium	pH 1.2 (hydrochloric acid buffer)	Volume	(b) (4)

Time [h]	0	1	2	4	7	9	12	24
% Released								
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	45	59	70	76	78	80	84
Std. Dev.	0	0	0	0	0	0	0	0

Batch	C0002AL0AT (4.6 mg/24 hr)	Apparatus	Rotating Cylinder
Medium	pH 1.2 (hydrochloric acid buffer)	Volume	500 ml

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	27	43	63	77	83	87	92
Std. Dev.	0	1	1	1	1	1	1	1

Batch	Exelon #1200BA (4.6 mg/24 hr)	Apparatus	(b) (4)
Medium	pH 1.2 (hydrochloric acid buffer)	Volume	(b) (4)

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	48	62	72	78	81	83	86
Std. Dev.	0	1	1	1	1	1	1	1

Reviewer's note: there are 2 dissolution data tables on individual units for the reference 4.6 mg/24 hr strength (lot # 1200BA) in (b) (4) and not individual unit table on 4.6 mg/24 hr strength of the reference product in (b) (4). This is probably a typographical error.

Batch	C0004AL0AU (9.5 mg/24 hr)	Apparatus	(b) (4)
Medium	pH 1.2 (hydrochloric acid buffer)	Volume	(b) (4)

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	25	40	60	76	81	86	90
Std. Dev.	0	1	1	1	2	2	2	3

Batch	Exelon #1401B (9.5 mg/24 hr)	Apparatus	(b) (4)
Medium	pH 1.2 (hydrochloric acid buffer)	Volume	(b) (4)

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	47	61	72	77	79	81	83
Std. Dev.	0	0	0	0	0	1	1	2

Batch	C0004AL0AU (9.5 mg/24 hr)	Apparatus	Rotating Cylinder
Medium	pH 1.2 (hydrochloric acid buffer)	Volume	500 ml

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	27	44	64	80	86	90	96
Std. Dev.	0	1	2	2	3	3	3	4

Batch	Exelon #1401B (9.5 mg/24 hr)	Apparatus	(b) (4)
Medium	pH 1.2 (hydrochloric acid buffer)	Volume	(b) (4)

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean								
Std. Dev.	0	0	0	0	1	1	1	1

Reviewer note: there are 2 dissolution data tables on individual units for the reference 9.5 mg/24 hr strength (lot # 1401B) in (b) (4) and not individual unit table on 9.5 mg/24 hr strength of the reference product in (b) (4). This is probably a typographical error.

Batch	C0002AL0AT (4.6 mg/24 hr)	Apparatus	(b) (4)
Medium	pH 4.5 (acetate buffer)	Volume	(b) (4)

Time [h]	0	1	2	4	7	9	12	24
% Released								
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	23	37	56	71	77	81	86
Std. Dev.	0	0	0	0	0	0	0	1

Batch	Exelon #1200BA (4.6 mg/24 hr)	Apparatus	(b) (4)
Medium	pH 4.5 (acetate buffer)	Volume	(b) (4)

Time [h]	0	1	2	4	7	9	12	24
% Released								
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	41	54	65	71	74	76	82
Std. Dev.	0	0	0	0	1	1	1	1

Batch	C0002AL0AT (4.6 mg/24 hr)	Apparatus	Rotating Cylinder
Medium	pH 4.5 (acetate buffer)	Volume	500 ml

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	25	40	60	75	81	85	91
Std. Dev.	0	1	1	1	1	1	1	1

Batch	Exelon #1200BA (4.6 mg/24 hr)	Apparatus	Rotating Cylinder
Medium	pH 4.5 (acetate buffer)	Volume	500 ml

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	44	57	67	73	75	78	83
Std. Dev.	0	1	1	1	1	1	1	1

Batch	C0004AL0AU (9.5 mg/24 hr)	Apparatus	(b) (4)
Medium	pH 4.5 (acetate buffer)	Volume	(b) (4)

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	23	38	58	74	79	84	88
Std. Dev.	0	0	1	1	1	1	1	2

Batch	Exelon #1401B (9.5 mg/24 hr)	Apparatus	(b) (4)
Medium	pH 4.5 (acetate buffer)	Volume	(b) (4)

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	42	55	66	73	75	77	83
Std. Dev.	0	0	0	0	0	0	0	1

Batch	C0004AL0AU (9.5 mg/24 hr)	Apparatus	Rotating Cylinder
Medium	pH 4.5 (acetate buffer)	Volume	500 ml

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	26	42	62	77	82	87	92
Std. Dev.	0	1	1	1	2	2	2	2

Batch	Exelon #1401B (9.5 mg/24 hr)	Apparatus	Rotating Cylinder
Medium	pH 4.5 (acetate buffer)	Volume	500 ml

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	45	59	70	76	79	81	87
Std. Dev.	0	1	0	0	1	1	1	1

Batch	C0002AL0AT (4.6 mg/24 hr)	Apparatus	(b) (4)
Medium	pH 6.8 (phosphate buffer)	Volume	(b) (4)

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	19	33	55	71	77	84	86
Std. Dev.	0	3	5	2	2	1	3	3

Batch	Exelon #1200BA (4.6 mg/24 hr)	Apparatus	(b) (4)
Medium	pH 6.8 (phosphate buffer)	Volume	(b) (4)

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	38	58	70	76	78	81	85
Std. Dev.	0	7	2	0	1	1	1	1

Batch	C0002AL0AT (4.6 mg/24 hr)	Apparatus	Rotating Cylinder
Medium	pH 6.8 (phosphate buffer)	Volume	500 ml

Time [h]	0	1	2	4	7	9	12	24
% Released								
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	24	38	58	74	80	85	91
Std. Dev.	0	1	1	1	1	1	1	2

Batch	Exelon #1200BA (4.6 mg/24 hr)	Apparatus	Rotating Cylinder
Medium	pH 6.8 (phosphate buffer)	Volume	500 ml

Time [h]	0	1	2	4	7	9	12	24
% Released								
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	47	61	71	77	80	82	87
Std. Dev.	0	1	1	1	1	1	1	1

Batch	C0004AL0AU (9.5 mg/24 hr)	Apparatus	(b) (4)
Medium	pH 6.8 (phosphate buffer)	Volume	(b) (4)

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	23	37	57	73	79	84	89
Std. Dev.	0	1	1	1	1	1	1	2

Batch	Exelon #1401B (9.5 mg/24 hr)	Apparatus	(b) (4)
Medium	pH 6.8 (phosphate buffer)	Volume	(b) (4)

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	43	62	73	80	82	84	89
Std. Dev.	0	7	1	1	0	0	0	1

Batch	C0004AL0AU (9.5 mg/24 hr)	Apparatus	Rotating Cylinder
Medium	pH 6.8 (phosphate buffer)	Volume	500 ml

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	25	40	61	76	82	86	91
Std. Dev.	0	1	1	1	1	1	1	1

Batch	Exelon #1401B (9.5 mg/24 hr)	Apparatus	Rotating Cylinder
Medium	pH 6.8 (phosphate buffer)	Volume	500 ml

Time [h]	0	1	2	4	7	9	12	24
	% Released							
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	0	49	63	74	80	82	85	89
Std. Dev.	0	0	0	0	0	0	0	0

III. Major amendment of January 22, 2013

In a major amendment dated January 22, 2013 the firm added a 13.3 mg/24 hr strength to the application. In the cover letter dated January 22, 2013 the firm has stated the following:

“In the Original ANDA, Alvogen proposed to utilize USP dissolution (b) (4) for the *in-vitro* drug release testing of Rivastigmine Transdermal System, 4.6 mg/24 hr and 9.5 mg/24 hr. Due to the size of the 13.3 mg/24 hr strength patch, it is not feasible to utilize USP dissolution (b) (4) for the *in-vitro* drug release test. The *in-vitro* drug release testing for all strengths of Rivastigmine Transdermal System will be performed utilizing dissolution apparatus 6. Additionally, the FDA recommended dissolution test method for Rivastigmine Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr and 13.3 mg/24 hr states to utilize USP apparatus 6. No system or chromatographic changes to the drug release method have been made. Also the specification limits proposed in the Original ANDA remain unchanged.”

In the major amendment of January 22, 2013 the firm submitted the following dissolution testing results for the 13.3 mg/24 hr strength and revised dissolution summary table that includes summary data for all 3 strengths.

13.3 mg/24 hour (test product)

Trial: C0014AL0BC NaCl
Apparatus: (b) (4)
Medium: NaCl
Volume [ml]: 500.00
Method: According to PV P251 V02 in combination with trial protocol dated 26.10.12

Patch Area [cm²]: 13.8
Area weight backingfoil [g/m²]: (b) (4)
Target matrix weight [mg/ TDS]: (b) (4)
API Amount [%]: (b) (4)

time [h]	0	1	2	4	7	9	12	24		
	Amount released [%]									
1	(b) (4)									
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Mean	0.00	22.29	37.79	59.74	77.86	84.41	90.02	95.84		
Standarddeviation	0.00	0.29	0.36	0.39	0.81	1.16	1.55	1.58		

13.3 mg/24 hour (reference product)

Trial:

Apparatus:

Medium:

Volume [ml]:

Method

Exelon #2302A NaCl
(b) (4)

NaCl

500.00

gem. PV P251 V02 in Kombination mit Versuchsplan
vom 26.10.12

Patch Area [cm²]:

Area weight backingfoil [g/m²]:

Target matrix weight [mg/ TDS]

API Amount [%]:

15

(b) (4)

time [h]	0	1	2	4	7	9	12	24		
	Amount released [%]									
1	(b) (4)									
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Mean	0.00	39.75	56.10	68.46	75.33	78.07	81.09	87.04		
Standarddeviation	0.00	0.73	0.55	0.64	0.64	0.76	0.77	0.71		

Since this is an extended release drug product, the firm also conducted dissolution testing in multimedia.

13.3 mg/24 hour (test product)

Trial:	C0014AL0BC pH 1.2	Patch Area [cm²]:	13,8
Apparatus:	(b) (4)	Area weight backingfoil [g/m²]:	(b) (4)
Medium:	Hydrochloric acid buffer pH 1.2	Target matrix weight [mg/ TDS]	(b) (4)
Volume [ml]:	500.0	API Amount [%]:	(b) (4)
Method	According to PV P251 V02 in combination with trial protocol dated 26.10.12		

time[h]	0	1	2	4	7	9	12	24			
	Amount released [%]										
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Mean	0,00	27,59	44,66	66,85	83,56	89,03	93,43	97,59			
Standarddeviation	0,00	0,78	1,14	1,32	1,12	1,21	0,95	1,15			

13.3 mg/24 hour (reference product)

Trial: Exelon #2302A pH 1,2
 Apparatus: (b) (4)
 Medium: Hydrochloric acid buffer pH 1,2
 Volume [ml]: 500,00
 Method: According to PV P251 V02 in combination with trial protocol dated 26.10.12

Patch Area [cm²]: 15
 Area weight backingfoil [g/m²]: (b) (4)
 Target matrix weight [mg/ TDS]
 API Amount [%]:

time [h]	0	1	2	4	7	9	12	24			
	Amount released [%]										
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Mean											
Standarddeviation	0,00	0,96	0,57	0,37	0,28	0,24	0,34	0,46			

13.3 mg/24 hour (test product)

Trial: C0014AL0BC pH 4.5
Apparatus: (b) (4)
Medium: Acetate buffer pH 4.5
Volume [ml]: 500.00
Method: According to PV P251 V02 in combination with trial protocol dated 26.10.12

Patch Area [cm²]: 13.8
Area weight backingfoil [g/m²]: (b) (4)
Target matrix weight [mg/ TDS]: (b) (4)
API Amount [%]: (b) (4)

time [h]	0	1	2	4	7	9	12	24		
	Amount released [%]									
1	(b) (4)									
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Mean	0.00	25.02	42.25	65.37	82.04	87.27	90.94	94.85		
Standarddeviation	0.00	0.49	0.65	0.85	0.54	0.78	0.65	0.77		

13.3 mg/24 hour (reference product)

Trial: Exelon #2302A pH 4,5
Apparatus: (b) (4)
Medium: Acetate buffer pH 4,5
Volume [ml]: 500.00
Method: According to PV P251 V02 in combination with trial protocol dated 26.10.12

Patch Area [cm²]: 15
Area weight backingfoil [g/m²]: (b) (4)
Target matrix weight [mg/ TDS]: (b) (4)
API Amount [%]: (b) (4)

time [h]	0	1	2	4	7	9	12	24		
	Amount released [%]									
1	(b) (4)									
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Mean	0.00	42.43	55.79	66.42	72.54	74.72	77.17	82.64		
Standarddeviation	0.00	0.30	0.26	0.23	0.33	0.36	0.38	0.40		

13.3 mg/24 hour (test product)

Trial: C0014AL0BC pH 5.5
 Apparatus: (b) (4)
 Medium: (b) (4)
 Volume [ml]:
 Method: According to PV P251 V02 in combination with trial protocol dated 26.10.12

Patch Area [cm²]: 13.8
 Area weight backingfoil [g/m²]: (b) (4)
 Target matrix weight [mg/ TDS]
 API Amount [%]:

time [h]	0	1	2	4	7	9	12	24		
	Amount released [%]									
1	(b) (4)									
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Mean	0.00	25.63	42.16	64.60	82.00	87.90	92.46	96.84		
Standarddeviation	0.00	0.59	0.67	0.64	0.59	0.58	0.57	1.17		

13.3 mg/24 hour (reference product)

Trial: Exelon #2302A pH 5.5
 Apparatus: (b) (4)
 Medium: (b) (4)
 Volume [ml]:
 Method: According to PV P251 V02 in combination with trial protocol dated 26.10.12

Patch Area [cm²]: 15
 Area weight backingfoil [g/m²]: (b) (4)
 Target matrix weight [mg/ TDS]
 API Amount [%]:

time[h]	0	1	2	4	7	9	12	24		
	Amount released [%]									
1	(b) (4)									
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Mean	0.00	49.86	64.57	74.99	81.21	83.24	85.56	89.92		
Standard deviation	0.00	0.44	0.42	0.62	0.66	0.79	0.79	0.65		

13.3 mg/24 hour (test product)

Trial: C0014AL0BC pH 6.8
 Apparatus: (b) (4)
 Medium: Phosphate buffer pH 6.8
 Volume [ml]: 500.0
 Method: According to PV P251 V02 in combination with trial protocol dated 26.10.12

Patch Area [cm²]: 13,8
 Area weight backingfoil [g/m²]: (b) (4)
 Target matrix weight [mg/ TDS]: (b) (4)
 API Amount [%]: (b) (4)

time [h]	0	1	2	4	7	9	12	24		
	Amount released [%]									
1	(b) (4)									
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Mean	0,00	25,22	41,56	63,79	80,84	86,67	91,27	95,58		
Standarddeviation	0,00	0,67	0,72	0,83	0,84	1,00	1,06	1,42		

13.3 mg/24 hour (reference product)

Trial: Exelon #2302A pH 6.8
 Apparatus: (b) (4)
 Medium: Phosphate buffer pH 6.8
 Volume [ml]: 500.0
 Method: According to PV P251 V02 in combination with trial protocol dated 26.10.12

Patch Area [cm²]:
 Area weight backingfoil [g/m²]:
 Target matrix weight [mg/ TDS]:
 API Amount [%]:

15
 (b) (4)

time[h]	0	1	2	4	7	9	12	24			
	Amount released [%]										
1	(b) (4)										
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Mean	0,00	48,48	62,76	73,16	79,06	81,27	83,42	87,78			
Standarddeviation	0,00	0,48	0,44	0,32	0,31	0,30	0,32	0,43			

Reviewer notes

As it was the case in the original submission of June 12, 2012, in the major amendment of January 22, 2013 the dissolution method listed in the dissolution summary table does not match the dissolution method shown on dissolution data tables on individual units.

Method listed in the dissolution summary table submitted on January 22, 2013:

(b) (4)

*Apparatus and medium are the FDA recommended apparatus and medium but FDA recommended volume is 500 mL; rotation speed has not been specified

Method shown in dissolution data tables on individual units submitted on January 22, 2013:

Apparatus:		(b) (4)
Medium:		NaCl*
Volume:		500 mL
Temperature:		32 ± 0.5°C

*FDA recommended method specifies the medium as 0.9% NaCl; rotation speed has not been specified

The Quality Overall Summary report included in the January 22, 2013 still indicates that dissolution testing is conducted using USP (b) (4).

Furthermore, the data on the 4.6 mg/24 hr and 9.5 mg/24 hr strengths in the dissolution summary table submitted on January 22, 2013 is the same data in the dissolution summary table submitted in the original submission of June 12, 2012 and matches dissolution testing data reported in the dissolution summary tables on individual units using USP (b) (4) and not the FDA recommended method.

IV. Dissolution Method Validation

(b) (4)

*The Dissolution Method Validation Report does not specify the detection method

V. COMMENTS:

Although from the statement made in the cover letter it appears that the firm is proposing to use the FDA recommended method for all 3 strengths, in no place in the submission the firm has listed the dissolution testing method it intends to use for its product in its entirety and the dissolution methods listed in the dissolution summary table and dissolution data tables on individual dosage units do not match the FDA recommended method.

Therefore, for all 3 strengths (4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr), the firm needs to conduct dissolution testing on 12 individual units each of the test and reference products using the following FDA recommended dissolution method:

Medium:	0.9% NaCl
Volume:	500 mL
Apparatus:	Modified USP Type VI (Cylinder)
Speed:	50 rpm
Temperature:	32 °C

The firm needs to provide the rotation speed and complete information on the medium used in all dissolution summary tables and dissolution data tables on individual dosage units.

VI. DEFICIENCY COMMENTS:

1. The DB II acknowledges that per cover letter of the major amendment of January 22, 2013 the firm is proposing to use the FDA recommended dissolution apparatus, Modified USP Apparatus VI (Cylinder). However, the dissolution testing methods reported in dissolution summary table submitted on January 22, 2013 and dissolution data tables on the individual dosage units (submitted on June 12, 2012 for the 4.6 mg/ 24 hr and 9.5 mg/ 24 hr strengths and on January 22, 2013 for the 13.3 mg/24 hr strength) are different and neither one of these method matches the FDA recommended method. Additionally, the firm has not specified rotation speed. It is also noted that the data provided on the 4.6 mg/24 hr and 9.5 mg/24 hr strengths in the dissolution summary table (in the submission of January 22, 2013) are the data from dissolution testing conducted using firm's own proposed method in the submission of June 22, 2012 (b) (4). For all 3 strengths (4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr), the firm needs to conduct dissolution testing on 12 individual units each of the test and reference products using the following FDA recommended dissolution method:

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Data on individual unit, means, range and %CV including f2 similarity values and dissolution plots should be submitted. The dissolution testing method used should be clearly stated in all dissolution summary tables and dissolution data tables on individual dosage units.

2. The firm has not specified rotation speed for any of the multi media dissolution testing. The firm needs to provide this information and also submit dissolution summary tables for all multimedia dissolution testing.
3. The dissolution method validation report does not specify the detection method. The firm needs to specify the detection method.
4. The firm needs to submit the Certificate of Analysis (COA) for the 4.6 mg/24 hr (lot #1200BA), 9.5 mg/24 hr (lot # 1401B) and 13.3 mg/24 hr (lot # 2302A).

RECOMMENDATIONS:

The dissolution testing conducted is incomplete. The firm should conduct dissolution testing using the following FDA-recommended dissolution method.

Medium: 0.9% NaCl

Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Additionally, the firm should specify rotation speed used in multimedia testing and provide the dissolution summary table for multimedia testing.

BIOEQUIVALENCE DEFICIENCY (IES)

ANDA: 204403
APPLICANT: Alvogen Pine Brook, Inc.
DRUG PRODUCT: Rivastigmine Transdermal System; 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr

The Division of Bioequivalence II (DB II) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence study will be conducted later. The following deficiencies have been identified:

1. In the cover letter of the amendment of January 22, 2013, you have proposed to use the FDA recommended dissolution apparatus, Modified USP Apparatus VI (Cylinder), for all 3 strengths of the test product. However, the dissolution testing methods reported in the dissolution summary table submitted on January 22, 2013 and dissolution data tables on the individual dosage units (submitted on June 12, 2012 for the 4.6 mg/ 24 hr and 9.5 mg/ 24 hr strengths and on January 22, 2013 for the 13.3 mg/24 hr strength) are different, and neither one of these method matches the FDA recommended method. Additionally, you have not specified the rotation speed. Please also note that the data provided on the 4.6 mg/24 hr and 9.5 mg/24 hr strengths in the dissolution summary table (in the submission of January 22, 2013) are the data from dissolution testing conducted using your own proposed method submission dated June 12, 2012 (b) (4). Please conduct dissolution testing on 12 individual units each of the test and reference products for all 3 strengths (4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr) using the following FDA recommended dissolution method:

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Please submit data on individual unit, means, range and %CV including f2 similarity values and dissolution

plots. Please clearly state the dissolution testing method used in all dissolution summary tables and dissolution data tables on individual dosage units. Additionally, you may refer to the Agency's dissolution guidance on Rivastigmine Transdermal System at <http://www.accessdata.fda.gov/scripts/cder/dissolutio>.

2. Please specify the rotation speed and submit dissolution summary tables for all multimedia dissolution testing.
3. The dissolution method validation report does not specify the detection method. Please specify the detection method.
4. Please provide the Certificate of Analysis (COA) for the 4.6 mg/24 hr (lot #1200BA), 9.5 mg/24 hr (lot # 1401B) and 13.3 mg/24 hr (lot # 2302A) strengths of the reference product.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA: 204403; APPLICANT: Alvogen Pine Brook, Inc.; DRUG
PRODUCT: Rivastigmine Transdermal System; 4.6 mg/24hr, 9.5 mg/24hr, and 13.3
mg/24 hr

VII. OUTCOME

ANDA: 204403

Completed Assignment for 204403 ID: 19273

Reviewer: Raofi, Saeid

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Rivastigmine Transdermal System

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
19273	6/12/2012*	Dissolution Credit (DRGC)	Dissolution Review for Dissolution-Only Credit	1	1
19273	1/22/2013*	Dissolution Credit (DRGC)	Dissolution Review for Dissolution-Only Credit	1	1
				Total:	2

**Please note that in the dissolution assignment list made on February 26, 2013, contained the dissolution on the 4.6 mg/24hr, 9.5 mg/24hr strengths as part of the original ANDA submission. As noted in the review, the 13.3 mg/24 strength was submitted in an amendment.*

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/s/

SAEID RAOFI
03/15/2013

CHANDRA S CHAURASIA
03/15/2013

BARBARA M DAVIT
03/23/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 204403

OTHER REVIEWS

INFORMATIONAL MEMORANDUM

NO ACTION INDICATED PADE EIR REVIEW

Date: March 15, 2017

To: Memo-to-file: Alvogen, Inc.

From: Kelley M. Simms, Consumer Safety Officer
Postmarketing Adverse Drug Experience (PADE) Compliance Team
PSB / DEPS / OSI / Office of Compliance / CDER

Subject: Review of Establishment Inspection Report (EIR) for PADE Inspection

General Information

Firm: Alvogen, Inc.

FEI Number: 3008454186

FACTS Assignment Number: 11681626

Drugs: See Appendix A

PAC Code: 53001A (CDER requested)

Priority: Work Plan

Inspection Dates: (b) (4)

Date EIR Received: 2/10/2017

Firm Response Date: N/A

District Office: New Jersey

District Classification: NAI

Center Classification: NAI

OSI/PADE Compliance Team review of the Establishment Inspection Report (EIR), and supporting evidence was completed for an inspection conducted in accordance with CPGM 7353.001, “Postmarketing Surveillance and Epidemiology: Human Drug and Therapeutic Biological Products.”

I. Background

Alvogen, Inc. (Alvogen), Almatica Pharma, Inc., Norwich Pharmaceuticals, Inc., and Alvogen Pine Brook LLC are all subsidiaries of Alvogen Group, Inc. (a U.S. corporation). Furthermore, the U.S. Corporation Alvogen Group, Inc. is a subsidiary of Alvogen Lux Holdings S.a.r.l (Lux) located in Luxembourg.

Alvogen Malta Operations Ltd, also a subsidiary of Lux, holds certain NDAs and ANDAs including, but not limited to, atenolol (Tenormin), budesonide, carbidopa, disulfiram, exemestane, and felbamate. However, the products are marketed in the U.S. by Alvogen (if generic) and Almatica (if brand) pursuant to a service agreement. The applicant is responsible for all regulatory submissions.

Similarly, Alvogen Group, Inc. signed a deal with Lotus Pharmaceuticals (Lotus), a firm with headquarters in China, in 2014 allowing Alvogen to partially acquire Lotus. Alvogen is the U.S. Agent whereas Lotus is responsible for regulatory submissions of its approved products. Additionally, on March 4, 2016, Alvogen Group, Inc. acquired County Line Pharmaceuticals, LLC (County Line) which is still listed as the applicant holder for its acquired products.

II. Regulatory History

The following table summarizes the PADE inspection-related regulatory history for Alvogen:

INSP. ENTITY	FEI NO.	F.Y.	FIELD CLASS.	CTR. CLASS.	REG. ACTION
Alvogen, Inc.	3008454186	2014	NAI	NAI	None
Alvogen, Inc.	3008454186	2011	NAI	NAI	None

III. EIR Review

The FY2017 inspection included an assessment of compliance with PADE regulations, including, but not limited to, a review of written procedures, contracts and agreements, oversight of contractors, waivers, literature searches, periodic safety reports, 15-day Alert Reports, complaints, and training.

Norwich Clinical Service Pvt. Ltd. (NCS), located in Bangalore, India, performs PADE functions for Alvogen Group, and is a subsidiary of Lux. The PADE team's review of the safety data exchange agreement between Alvogen and NCS described that NCS shall maintain the centralized Global Safety Database for Alvogen products. No deficiencies were noted.

Late 15 day alerts were identified and reviewed by the investigator but not collected as exhibits. Additionally, the investigator reviewed Alvogen's deviation process for ICSRs but no specific deviations were included as exhibits. The investigator did not note any deficiencies and did not issue a Form FDA 483; however, the investigators discussed two items with the firm.

Discussion items:

1. Late aggregate periodic safety reports since the last inspection, reasons for late reporting, and deviation reports were collected and reviewed by the investigator. The evidence supports this discussion item. Actions taken prior to the inspection to prevent reoccurrence of late reporting should be assessed during the next inspection..

2. Alvogen's (b) (4) Product Quality, Section 5.1 states that product quality complaints received by Alvogen (without report of an adverse drug experience) will not be forwarded to NCS. This differs from the actual practice, and the evidence supports this discussion item. However, prior to the closeout meeting the firm updated (b) (4) to reflect their current processes.

IV. Recommendation

The PADE team recommends the next PADE inspection during FY2020. During the next inspection consider assessing and collecting any corrective actions implemented for late ICSR submission.

Appendix A: Products reviewed during the inspection

(A)NDA#	Product
020198	Adalat CC (nifedipine) oral extended release tablet
018760	Tenoretic (atenolol/chlorthalidone) oral tablet
018240	Tenormin (atenolol) oral tablet
016620	Macrochantin (nitrofurantoin) oral capsule
020064	Macrobid (nitrofurantoin) oral capsule
016151	Urex (methenamine) 1gm oral tablet
019888	Zestoretic (hydrochlorothiazide/lisinopril) oral tablet
019777	Zestril (lisinopril) oral tablet
205120	Butalbital/acetaminophen oral tablet
202684	Levonorgestrel oral tablet
205756	Methylphenidate chewable oral tablet
205055	Nateglinide oral tablet
204403	Rivastigmine extended release transdermal film
202677	Oxycodone/acetaminophen oral tablet
204621	Nevirapine extended release tablet
071514	Trazodone oral tablet
062800	Clindamycin injection
062801	Clindamycin injection
062943	Clindamycin injection
091681	Disulfiram oral tablet
090906	Levetiracetam oral tablet
202116	Oxycodone oral tablet

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/s/

KELLEY M SIMMS
03/15/2017

RICHARD A ABATE
03/15/2017

**REGULATORY PROJECT MANAGER'S CLINICAL SITE SELECTION REVIEW FOR OFFICE OF
SCIENTIFIC INVESTIGATIONS (OSI) INSPECTION**

ANDA#	204403
Product	Rivastigmine Transdermal System Extended-release Film, 4.6 mg/24 hr and 9.5 mg/24 hr
Sponsor	Alvogen Pine Brook, Inc.
Study Number and Title	C10-1870 (R10-1318, S11-0069) A Multiple Site Study to Evaluate the Irritation and Sensitization Potential of Repeat Applications of Rivastigmine 4.6 mg/24 hours Patch (Transdermal System) versus Exelon 4.6 mg/24 hours Patch (Rivastigmine Transdermal System) in Normal Healthy Volunteers
Study Dates	First Patient Enrolled: January 16, 2012 Last Patient Completed: February 25, 2012
Submission Date	June 12, 2012
DCR ANDA Reviewer	Daiva Shetty, M.D.
Inspection Requestor	Nitin K. Patel, Pharm.D. Medical Affairs Coordinator, Division of Clinical Review (DCR) Office of Generic Drugs
Date of Review	September 20, 2013
Approving Official	John R. Peters, M.D. Director, Division of Clinical Review Office of Generic Drugs

This review is an addendum to the Regulatory Project Manager's Clinical Site Selection review dated December 3, 2012.

See Attachment for List of Investigators and Sites

SITE NUMBER	HIGH ENROLLMENT PER PROTOCOL POPULATION	HIGH DROPOUTS/ EXCLUSIONS	NO INSPECTION HISTORY	LAST INSPECTION VAI & > 5YR	HAS PRIOR INSPECTION HISTORY	DATA UNACCEPTABLE IN PRIOR INSPECTION
01	✓				2/3/12: VAI for ANDA 202346	
02	✓				9/7/12: Pending for ANDA (b) (4)**	

** On May 21, 2013, OSI provided their evaluation of the FDA audit of the clinical portions of two studies for ANDA (b) (4), conducted at PRACS Institute (Cetero Research, Principal Investigator: James C. Freeman), St. Charles, MO, during (b) (4) by ORA investigators Kathleen B. Swat and Karen M. Montgomery (Kansas District Office). **OSI classified this clinical site as OAI** and provided the following conclusions:

-
-



Because of these findings, DCR will request a For-Cause inspection for Dr. James C. Freeman (Site #02), at this time.

ATTACHMENT

SITE NUMBER	Principal Investigator	Number of Subjects
01	Alan K. Copa, Pharm.D. Cetero Research 4801 Amber Valley Parkway Fargo, ND 58104	140
02	James C. Freeman, M.D. Cetero Research – St. Charles 400 Fountain Lakes Blvd. St. Charles, MO 63301	140

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/s/

NITIN K PATEL
09/20/2013

JOHN R PETERS
09/20/2013

**REGULATORY PROJECT MANAGER'S CLINICAL SITE SELECTION REVIEW FOR OFFICE OF
SCIENTIFIC INVESTIGATIONS (OSI) INSPECTION**

ANDA#	204403
Product	Rivastigmine Transdermal System Extended-release Film, 4.6 mg/24 hr and 9.5 mg/24 hr
Sponsor	Alvogen Pine Brook, Inc.
Study Number and Title	C10-1870 (R10-1318, S11-0069) A Multiple Site Study to Evaluate the Irritation and Sensitization Potential of Repeat Applications of Rivastigmine 4.6 mg/24 hours Patch (Transdermal System) versus Exelon 4.6 mg/24 hours Patch (Rivastigmine Transdermal System) in Normal Healthy Volunteers
Study Dates	First Patient Enrolled: January 16, 2012 Last Patient Completed: February 25, 2012
Submission Date	June 12, 2012

See Attachment for List of Investigators and Sites

SITE NUMBER	HIGH ENROLLMENT PER PROTOCOL POPULATION	HIGH DROPOUTS/ EXCLUSIONS	NO INSPECTION HISTORY	LAST INSPECTION VAI & > 5YR	HAS PRIOR INSPECTION HISTORY	DATA UNACCEPTABLE IN PRIOR INSPECTION
01	✓				2/3/12: VAI for ANDA 202346	
02	✓				9/7/12: Pending for ANDA (b) (4)	

Date of Review: November 30, 2012

Primary Reviewer: Nitin K. Patel, Pharm.D., Medical Affairs Coordinator, Division of Clinical Review

Secondary Reviewer: John R. Peters, M.D., Director, Division of Clinical Review, Office of Generic Drugs

RECOMMENDATION:

Dr. Alan K. Copa (Site #01) has a satisfactory prior inspection history (see details below) and a new inspection will not be requested at this time.

ANDA#	202346
Product	Lidocaine Topical Patch, 5%
Principal Investigator	Alan K. Copa, Pharm.D. Cetero Research 4801 Amber Valley Parkway Fargo, ND 58104
Study Number(s)	LIDO-1046 (218 subjects); LIDO-1044 (24 subjects)
Date of OSI Report and Conclusion	February 3, 2012 VAI – FDA Form 483 not issued. OSI recommends that the studies be accepted for review

Dr. James C. Freeman (Site #02) has a pending inspection history (see details below) and a new inspection will not be requested at this time.

ANDA#	(b) (4)
Product	(b) (4)
Principal Investigator	James C. Freeman, M.D. Cetero Research – St. Charles 400 Fountain Lakes Blvd. St. Charles, MO 63301
Study Number(s)	(b) (4)
Date of OSI Inspection Request	September 7, 2012

ATTACHMENT

SITE NUMBER	Principal Investigator	Number of Subjects
01	Alan K. Copa, Pharm.D. Cetero Research 4801 Amber Valley Parkway Fargo, ND 58104	140
02	James C. Freeman, M.D. Cetero Research – St. Charles 400 Fountain Lakes Blvd. St. Charles, MO 63301	140

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/s/

NITIN K PATEL
11/30/2012

JOHN R PETERS
12/03/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 204403

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

Approval Type: ☒ FULL APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH)		
RPM: Potter Team:		Approval Date: 9/3/2015
☐ PI ☐ PII ☐ PIII ☒ PIV (<i>eligible for 180 day exclusivity</i>) ☐ Yes ☒ No ☐ MOU ☒ RX or ☐ OTC		
ANDA #: 204403 Applicant: Alvogen Pine Brook, Inc. Established Product Name: Rivastigmine Transdermal System, 4.6 mg/24 hr and 9.5 mg/24 hr		
Basis of Submission (RLD): Exelon NDA#22083 <i>(Is ANDA based on an approved Suitability Petition?)</i> ☐ Yes ☒ No		
Does the ANDA contain REMS? ☐ Yes ☒ No <i>(If YES, initiate approval action 6 weeks prior to target action date)</i>		
Regulatory Project Manager Evaluation:		Date: 8/24/2015
☒ Date last Complete Response (CR) letter was issued -- Date 7/25/2014 ☒ Previously reviewed and tentatively approved (if applicable) --- Date 8/31/2015		
Date of Application 6/12/2012	Original Received Date 6/12/2012	Date Acceptable for Filing 6/12/2012
YES	NO	
☒	☐	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A) Date of Acceptable Quality 6/29/2015 Date of Acceptable Dissolution 1/7/2015 Date of Acceptable Bioequivalence 12/19/2014 Date of Acceptable Labeling 7/21/2015 If applicable: Date of Acceptable Microbiology N/A Date of Acceptable Clinical Review 7/20/2015 Date of Acceptable REMS N/A
☐	☒	Are consults pending for any discipline?
☒	☐	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES → Verify a second filing review was completed and that all disciplines completed new reviews ☒
☐	☒	Is there a pending Citizen Petition (CP)?
☒	☐	Overall OC Recommendation is acceptable (EES is acceptable) Date Acceptable: _____ Re-evaluation Date: 8/1/2016
☒	☐	OSI Clinical Endpoint and Bioequivalence Site Inspections are acceptable
☒	☐	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff (OGDREQUEST) 30 to 60 days prior to approval, Date emailed
Draft Approval/Tentative Approval Letter		
☒	☐	Approval/Tentative Approval letter is drafted and uploaded to the Final Decision task
Review Discipline/Division Endorsements		
☒	☐	Division of Legal and Regulatory Support Endorsement completed, Date 9/3/2015
☒	☐	Paragraph IV Evaluation completed (if applicable), Date 9/3/2015
☒	☐	Quality Endorsement completed, Date 9/3/2015
☒	☐	Bioequivalence Endorsement completed, Date 9/3/2015
☒	☐	Labeling Endorsement completed, Date 9/3/2015
☐	☐	REMS Endorsement (if applicable), Date N/A
RPM Team Leader Endorsement and Action Package Verification		
☒	☐	RPM Team Leader Endorsement completed, Date 9/3/2015
Final Decision and Letter Sign-off		
☒	☐	Final Decision recommending approval/tentative approval completed, Date 9/3/2015
☒	☐	Approval/Tentative Approval letter electronically signed, Date: 9/3/2015
Project Close-Out		
☒	☐	Notify applicant of approval and provide a courtesy copy of the electronically signed letter
☐	☒	Is there a Post Marketing Agreement (PMA)? IF YES → Send email to PMA coordinator, Date emailed
☒	☐	Email OGD Approval distribution list (CDER-OGDAPPROVALS) with approval information



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ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 9/3/2015

Name/Title: IM for MHS

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)	Pediatric Exclusivity System RLD = _____ NDA# _____ Date Checked _____ Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days: Yes ☒ No ☐ Has case been settled: Yes ☒ No ☐ Date settled: 7/7/2014 Is applicant eligible for 180 day YES/NO Is a forfeiture memo needed: Yes ☒ No ☐ If yes, has it been completed	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐	
Date of latest Labeling Review/Approval Summary	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒	
Type of Letter: ☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER:	
Comments: BOS = Exelon Patch (NDA 22083) Application submission 6/12/2012 for the 4.6 mg and 9.5 mg strengths with a PIII certification to the '807 patent and PIV certifications to the '176, '023 and '031 patents. Acknowledgment letter signed 11/19/2012. Applicant sued on the '023 and '031 patents in USDC of Delaware 1/4/2013 and converted the certification of the '176 patent from PIV to PIII. NSA received 1/22/2013 for the 13.3 mg strengths with a PIII certification to the '176 patent and PIV certifications to the '023 and '031 patents. (b) (4) of the proposed labeling and information associated with the NS would remain and Alvogen would not market until expiration of the exclusivity. Suit filed 3/7/2013 in USDC of Delaware on the '023 and '031 patents. This suit is for the 13.3 mg strength. 7/7/2014 Alvogen and Novartis entered into a Joint Stipulation of Dismissal for the 13.3 mg strength and a Judgment of Noninfringement in favor of Alvogen for the 4.6 mg and 9.5 mg strengths. On 7/22/2015, a Tentative Approval was issued for all three strengths with the reason being the unexpired NS exclusivity which had been determined could not be carved out as well as Alvogen's certification that did not seek approval until after the exclusivity expires, 8/31/2015. It had also been determine the NS exclusivity prevented approval of the 4.6 mg and 9.5 mg strengths. (b) (4) is the first application for the 4.6 mg and 9.5 mg strengths. However, they did not secure a TA within 40 months of their original resubmission (original RTR'd). A forfeiture analysis (8/28/2015) has been performed and finds the 180-day exclusivity is NOT forfeited for the two lower strengths. Alvogen is the first-to-file for the 13.3 mg strength. They were able to secure a TA on this strength within 30 months of the submission to secure the exclusivity. With the expiration of the NS exclusivity, this ANDA is eligible for Full Approval on the 13.3 mg strength with 180-day exclusivity and eligible for Tentative Approval only on the 4.6 mg and 9.5 mg strengths due to the 180-day held by (b) (4)	



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Update 9/3/2017: After the ARS and TA/AP letter had been generated, the Agency learned the Court of Appeals FC issued an opinion 5/21/2015 affirming the lower court's decision the claims are not invalid. With this decision, (b) (4) no longer has a PIV certification to the '023 and '031 patents and 180-day exclusivity is forfeited (see memo in (b) (4)). Of note, (b) (4) has not provided this documentation as of 9/3/2015.

Alvogens ANDA is now eligible for Full Approval on all strengths with 180-day exclusivity granted on the 13.3 mg/24 hour strength.



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2. **Paragraph IV Evaluation (for ANDAs with PIV certifications or other controversial regulatory issues)**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

3. **Quality Endorsement by the Office of Pharmaceutical Science**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

4. **Bioequivalence Endorsement**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

5. **Labeling Endorsement**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

6. **REMS Endorsement**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

7. **RPM Team Leader Endorsement**

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform



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8. Final Decision

Date: 9/3/2015
Name/Title: wpr

Para.IV Patent Cert: Yes No
Pending Legal Action: Yes No
Petition: Yes No
Entered to APTrack database
GDUFA User Fee Obligation Status Met Unmet
Press Release Acceptable
First Generic Approval
PD or Clinical for BE
Special Scientific or Reg. Issue

Date PETS checked for first generic drug _____

Comments:

BOS = Exelon Patch (NDA 22083). The applicant provided PIV certifications to the '023 and '031 patents. They complied with the notification requirements and were sued within the 45 day period. The applicant then notified OGD that this litigation was dismissed. A Tentative Approval letter was issued for all three strengths with the reason being the unexpired NS exclusivity which had been determined could not be carved out as well as Alvogen's certification that they do not seek approval until after the exclusivity expires, 8/31/2015. It had also been determine the NS exclusivity prevented approval of the 4.6 mg and 9.5 mg strengths. ^{(b) (4)} is the first application for the 4.6 mg and 9.5 mg strengths. However, they did not secure a TA within 40 months of their original resubmission. A forfeiture analysis (8/28/2015) has been performed and finds the 180-day exclusivity is NOT forfeited for the two lower strengths. Alvogen is the first-to-file for the 13.3 mg strength. They were able to secure a TA on this strength within 30 months of the submission to secure the exclusivity. With the expiration of the NS exclusivity, this ANDA is eligible for Full Approval Chemistry acceptable 6/26/2015. QE 8/25/2015. Bio/clinical acceptable 12/19/2014 and OSI report 7/21/2015. Labeling acceptable 7/17/2015. Inspection report overall acceptable checked 8/31/2015. This is eligible for full approval.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION	
TO (Division/Office): OND/DNP (Teresa Wheelous, RPM)		FROM: Carrie Lemley, Labeling PM Office of Generic Drugs/Div. of Labeling	
DATE July 1, 2015	ANDA NO. 204403	TYPE OF DOCUMENT (Choose One) ☒ ORIGINAL ANDA ☐ SUPPLEMENT TO ANDA	DATE OF DOCUMENT: Template prepared by OGD based on NDA 22083/S-20
NAME OF DRUG Rivastigmine	PRIORITY CONSIDERATION (Choose One) ☒ (HIGH) ☐ Low	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Choose One) Requested Due Date: 7/15/15 (Generic Forfeiture Date 7/22)
NAME OF FIRM: Alvogen			
REASON FOR REQUEST			
I. GENERAL			
☐ NEW PROTOCOL ☐ PROGRESS REPORT ☐ NEW CORRESPONDENCE ☐ DRUG ADVERTISING ☐ ADVERSE REACTION REPORT ☐ MANUFACTURING CHANGE/ADDITION ☐ MEETING PLANNED BY ☐ PRE--NDA MEETING ☐ END OF PHASE II MEETING ☐ RESUBMISSION ☐ SAFETY/EFFICACY ☐ PAPER NDA ☐ CONTROL SUPPLEMENT ☐ RESPONSE TO DEFICIENCY LETTER ☐ FINAL PRINTED LABELING ☐ LABELING REVISION (carton/container label) ☐ ORIGINAL NEW CORRESPONDENCE ☐ FORMULATIVE REVIEW ☒ OTHER (SPECIFY BELOW): Labeling Template Carve-out **See Attached Documents.			
II. BIOMETRICS			
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH	
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):		☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS			
☐ DISSOLUTION ☐ BIOAVAILABILITY STUDIES ☐ PHASE IV STUDIES		☐ DEFICIENCY LETTER RESPONSE ☐ PROTOCOL-BIOPHARMACEUTICS ☐ IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE			
☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below) ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY ☐ SUMMARY OF ADVERSE EXPERIENCE ☐ POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS			
☐ CLINICAL		☐ PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS:			
OGD is requesting this consult in order for a potential labeling carve-out for generic rivastigmine products to be evaluated by DNP to determine whether omission of the information protected by exclusivity would render generic products less safe or effective than the listed drug for the remaining, non-protected conditions of use. See attached word document. OGD will schedule a meeting to discuss the template if the division feels it would be helpful. Please email Carrie.Lemley@fda.hhs.gov if you would like a meeting next week.			
SIGNATURE OF REQUESTER		METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND ☒ DAARTS	
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER	

Labeling Carve-Out Consult

Innovator Product Name: Exelon (rivastigmine transdermal system) Patch, 4.6 mg/24 hrs, 9.5 mg/24 hrs, 13.3 mg/24 hrs

Background

The Reference Listed Drug, **Exelon** (NDA 022083) of Novartis Pharmaceuticals Corporation has received 3 years of Hatch-Waxman exclusivity for updates to the labeling in S-016 to reflect a new strength of 13.3 mg/24 hours for use in the previously approved indications for the treatment of mild to moderate dementia of the Alzheimer's type as well as for the treatment of mild to moderate dementia associated with Parkinson's disease. This exclusivity expires August 31, 2015.

The statute and regulations generally require abbreviated new drug applications (ANDAs) to have the same labeling as the labeling approved for the listed drug, but ANDA labeling can omit aspects of the listed drug's labeling that are protected by patent or by exclusivity, provided that such differences do not render the ANDA product less safe or effective than the listed drug for all remaining, non-protected conditions of use.

ANDA applicants for rivastigmine transdermal system that reference Exelon as their listed drug have proposed to [REDACTED] (b) (4)

[REDACTED] (b) (4) This would result in labeling for these products that would not reflect information indicating that patients can be increased to a maximum effective dose of 13.3 mg/24 hours for the treatment of mild to moderate dementia of the Alzheimer's type as well as for the treatment of mild to moderate dementia associated with Parkinson's disease. Given the progressive nature of these conditions, OGD is concerned that omitting the reference to the maximum dose of 13.3 mg/24 hours would render the generics less effective than Exelon. OGD thus believes that reference to the 13.3 mg/24 hours dose must be retained in ANDA labeling as omission of this information would result in labeling that renders the drugs less effective for the remaining non-protected conditions of use than Exelon.

Consult Question

OGD requests a consult on whether ANDAs for the drug product rivastigmine that reference Exelon (NDA 022083) as their basis of submission can permissibly carve-out the information added to the labeling for Exelon in S-016 related to the new strength of 13.3 mg/24 hours for use in the previously approved indications for the treatment of mild to moderate dementia of the Alzheimer's type as well as for the treatment of mild to moderate dementia associated with Parkinson's disease.

In particular, OGD seeks DNP's feedback on the following question:

1. Would omission of the protected information related to the 13.3 mg/24 hours strength render generic products less safe or effective than Exelon for the approved indications of treatment of mild to moderate dementia of the Alzheimer's type as and/or treatment of mild to moderate dementia associated with Parkinson's disease?

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/s/

CARRIE L LEMLEY
07/01/2015



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Post Complete Response Teleconference

Meeting Category: End of Review

Meeting Date and Time: June 12, 2015 9:15 A.M.

Application Number: 204403

Product Name: Rivastigmine Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr,
and 13.3 mg/24 hr.

Applicant Name: Alvogen Pine Brook, Inc.

Meeting Recorder: Andrew Potter

FDA ATTENDEES

Robert Berendt, Quality Assessment Lead

Caroline Stasinger, Branch Chief, Division of Modified Release Products, Branch I

Suneela Prodduturi, Chemistry Reviewer

Brijet Burton, Regulatory Business Project Manager

Nima Ossareh, Regulatory Business Project Manager

Andrew Potter, Regulatory Project Manager

Sarah Park, Labeling Team leader

James Barlow, Labeling Reviewer

Danielle Russell, Labeling Project Manager

APPLICANT ATTENDEES

Patricia Jaworski, Vice President Regulatory Affairs

Dr. Mayank Joshi, Vice President R&D USGx

Chandran Tiruvattar, Associate Director Regulatory Affairs

A. BACKGROUND

Purpose of meeting: To discuss CMC and Labeling issues with the applicant to help resolve the discrepancies in a timely manner.

Expected outcome for the meeting: Alvogen will become aware of deficiencies that will need to be corrected prior to approval.

B. DISCUSSION

1. DMF (b) (4)

Discussion:

We informed the applicant that DMF (b) (4) was recently found inadequate, and was notified on May 15, 2015 and the deficiencies would need to be addressed prior to approval. The applicant acknowledged the deficiencies and agreed to work with the DMF holder to resolve the deficiencies.

2. The applicant's response to the Question #10 from the IR Amendment

Discussion:

We informed the applicant they will need to update the backing membrane of the patch. (b) (4)
(b) (4) The agency will require the full drug name and strength for identification purposes. The applicant made several arguments including:

- Oral dosage forms usually never have the complete drug name
- Other patches have been approved without the full name and strength

We advised the applicant that we cannot comment on any other ANDAs and that the agencies current policy is exhibited by the Fentanyl Public Safety Notification of 2013. The applicant requested permission to make the changes to the patch and labeling post approval and to allow the patches that have already been manufactured to be marketed. The agency will consider the request and asked the applicant to submit their proposal and include the following information:

- A mock-up of the proposed backing membrane with the full drug name and strength and a commitment that the ink and font would not change
- The quantity of patches already produced and would potentially be marketed
- The date the patches were manufactured and the expiration date
- When the new patches with the updated drug name will be manufactured
- The list of documents that will need to be updated when the change to the backing membrane is made

3. Patient Information

Discussion:

We asked the applicant to describe the cover sheet that will be used for the patch. The cover sheet takes the place of the dimpled liner that the RLD uses, but functions in the same way.

Teleconference Meeting Minutes

The cover sheet is not addressed in the patient information. The applicant committed to adding a statement to the instructions for use to include (b) (4)

We also requested that the applicant make changes in the patient information guide. In order to be uniform throughout we asked the applicant to change the term (b) (4) to “protective liner”.

For both of these changes, the applicant requested the change to be made post approval. The applicant committed to submitting a mock-up for review and evaluation of the request.

4. Conclusion

Discussion:

We acknowledge the Target Action Date of June 15, 2015 will not be meet. The applicant will submit a formal proposal for the changes addressed during the teleconference regarding the print on the patch and the labeling and patient information. The applicant requested any additional information regarding the status of the other disciplines. The applicant was informed that the Bioequivalence portion is complete.



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ANDA 204403

**MEETING REQUEST GRANTED
WRITTEN RESPONSES ONLY**

Alvogen Pine Brook, Inc.
Attention: Patricia Jaworski
Vice President, Regulatory Affairs
10 Bloomfield Avenue
Pine Brook, NJ 07058

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 12, 2012, received June 12, 2012, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Rivastigmine Transdermal System, 4.6 mg/24 hour, 9.5 mg/24 hour, and 13.3 mg/24 hour.

Further reference is made to our Meeting Granted letter dated August 28, 2014, wherein we stated that written responses to your questions would be provided in lieu of a teleconference.

The enclosed document constitutes our written responses to the questions contained in your Post Complete Response Teleconference Meeting Request dated August 11, 2014.

If you have any questions, call Andrew Potter, Regulatory Project Manager at (240) 402-9266.

Sincerely,

{See appended electronic signature page}

Andrew Potter
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure:
Written Responses

WRITTEN RESPONSES

Meeting Type: Post Complete Response Teleconference Meeting
Meeting Category: End of Review

Application Number: 204403
Product Name: Rivastigmine Transdermal System, 4.6 mg/24 hour,
9.5 mg/24 hour and 13.3 mg/24 hour
Sponsor/Applicant Name: Alvogen Pine Brook, Inc.

1.0 BACKGROUND

In preparing to respond to the Complete Response Letter dated, July 25 2014, Alvogen Pine Brook, Inc., requested a Post Complete Response Teleconference for clarifications and instructions from the Agency for ANDA 204403 for Rivastigmine Transdermal System, 4.6 mg/24 hour, 9.5 mg/24 hour, and 13.3 mg/24 hour. It was determined that a written response would be the most appropriate means for responding to the meeting request.

2.0 QUESTIONS AND RESPONSES

2.1 CMC



(b) (4)

2.2 Dissolution

Question 1:

The Agency has stated the following within the Dissolution section of the referenced Complete Response Letter;

"However, please note that the dissolution specifications are set based on the data obtained on fresh bio lots and are not modified based on development, scale up or stability batch data ... "

We recognize that the Agency has raised this question twice and proposed these limits. However Alvogen strongly believes shelf-life data should be considered when establishing specification limits. The stability analysis takes into account a larger sample size of data which is more representative of the finished product. Can the Agency please provide their rationale for establishing the proposed specification limits?

The agency also stated in the referenced Complete Response Letter,

" ... recommendation of a range at the 24 hour time point is in accordance with USP Chapter 24 - Table 1. "

Would the Agency consider a revision to the proposed 24 hour time point specification range of (b) (4)%? Alvogen's Bioequivalence Amendment submitted on November 11, 2013 demonstrated a patch with an assay value at (b) (4)% would likely fail to meet the proposed dissolution criteria at 24 hours. As a result, the currently proposed 24 hour dissolution specification creates a tighter control than the acceptable Assay and Content Uniformity specifications.

FDA Response to Question 1:

The agency acknowledges your concerns regarding setting an upper limit for dissolution specification at the 24 hour time point and accepts your proposed specification of NLT (b) (4)% at the 24 hour time point. Please acknowledge the following FDA recommended dissolution method and specifications:

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications: (b) (4)
1 hour:
2 hours:
4 hours:
9 hours:
24 hours:

2.3 Labeling

Question 1:

3. Package Insert and Patient Information Leaflet

We note that revised package insert labeling has been recently approved for the reference listed drug, Exelon® Patch by Novartis (NDA 22-083/S-0 19; approved June 27,2013) and these revisions are protected by exclusivity. Please address how you will certify regarding this recent update.

Alvogen Question:

Alvogen asks whether it will suffice to submit an amended exclusivity statement to the ANDA, along with labeling amended in which there is a (b) (4)

(b) (4)

FDA Response to Question 1:

A labeling amendment with MOU certification and the protected information carved out would suffice.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DENISE T MCKAN
10/17/2014



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ANDA 204403

**MEETING REQUEST GRANTED
WRITTEN RESPONSES ONLY**

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Sincerely,

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Andrew Potter
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
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Enclosure:
Written Responses

WRITTEN RESPONSES

Meeting Type: Post Complete Response Teleconference Meeting
Meeting Category: End of Review

Application Number: 204403
Product Name: Rivastigmine Transdermal System, 4.6 mg/24 hour,
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Sponsor/Applicant Name: Alvogen Pine Brook, Inc.

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2.0 QUESTIONS AND RESPONSES

2.1 CMC



2.2 Dissolution

Question 1:

The Agency has stated the following within the Dissolution section of the referenced Complete Response Letter;

"However, please note that the dissolution specifications are set based on the data obtained on fresh bio lots and are not modified based on development, scale up or stability batch data ... "

We recognize that the Agency has raised this question twice and proposed these limits. However Alvogen strongly believes shelf-life data should be considered when establishing specification limits. The stability analysis takes into account a larger sample size of data which is more representative of the finished product. Can the Agency please provide their rationale for establishing the proposed specification limits?

The agency also stated in the referenced Complete Response Letter,

" ... recommendation of a range at the 24 hour time point is in accordance with USP Chapter 24 - Table 1. "

Would the Agency consider a revision to the proposed 24 hour time point specification range of (b) (4)%? Alvogen's Bioequivalence Amendment submitted on November 11, 2013 demonstrated a patch with an assay value at (b) (4)% would likely fail to meet the proposed dissolution criteria at 24 hours. As a result, the currently proposed 24 hour dissolution specification creates a tighter control than the acceptable Assay and Content Uniformity specifications.

FDA Response to Question 1:

The agency acknowledges your concerns regarding setting an upper limit for dissolution specification at the 24 hour time point and accepts your proposed specification of NLT (b) (4)% at the 24 hour time point. Please acknowledge the following FDA recommended dissolution method and specifications:

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications:

1 hour: (b) (4)
2 hours: (b) (4)
4 hours: (b) (4)
9 hours: (b) (4)
24 hours: (b) (4)

2.3 Labeling

Question 1:

3. Package Insert and Patient Information Leaflet

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(b) (4)

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/s/

DENISE T MCKAN
10/14/2014

POST CR MEETING REQUEST WRITTEN RESPONSES - BIOEQUIVALENCE

Meeting Type: Post Complete Response Teleconference Meeting
Meeting Category: End of Review

Application Number: 204403
Product Name: Rivastigmine Transdermal System, 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr
Sponsor/Applicant Name: Alvogen Pine Brook, Inc.

1 BACKGROUND

Alvogen Pine Brook Inc. requested a teleconference with the Agency to discuss the DB's proposed dissolution specifications that were communicated to the firm in the complete response letter of July 25, 2014 for Rivastigmine Transdermal System, 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr.

2 QUESTIONS AND RESPONSES

2.1. Bioequivalence

Firm's Question:

The Agency has stated the following within the Dissolution section of the referenced Complete Response Letter;

"However, please note that the dissolution specifications are set based on the data obtained on fresh bio lots and are not modified based on development, scale up or stability batch data ... "

We recognize that the Agency has raised this question twice and proposed these limits. However Alvogen strongly believes shelf-life data should be considered when establishing specification limits. The stability analysis takes into account a larger sample size of data which is more representative of the finished product. Can the Agency please provide their rationale for establishing the proposed specification limits?

The agency also stated in the referenced Complete Response Letter,

" ... recommendation of a range at the 24 hour time point is in accordance with USP Chapter 24 - Table 1. "

Would the Agency consider a revision to the proposed 24 hour time point specification range of (b) (4) %?

Alvogen's Bioequivalence Amendment submitted on November 11, 2013 demonstrated a patch with an assay value at (b) (4) % would likely fail to meet the proposed dissolution criteria at 24 hours. As a result, the currently proposed 24 hour dissolution specification creates a tighter control than the acceptable Assay and Content Uniformity specifications.

DB II Response:

The agency acknowledges your concerns regarding setting an upper limit for dissolution specification at the 24 hour time point and accepts your proposed specification of NLT (b) (4) % at the 24 hour time point. Please acknowledge the following FDA recommended dissolution method and specifications:

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications:

1 hour: (b) (4)
2 hours:
4 hours:
9 hours:
24 hours:

NOTE to PM: Do not include the following information into your memorandum to file.

3 ADDITIONAL ATTACHMENTS

3.1 Item 1

From: Anand, Om
Sent: Thursday, September 19, 2013 9:04 AM
To: Stier, Ethan
Cc: Anand, Om; Mahadevan, Chitra
Subject: RE:

Ethan:

Technically, it [REDACTED] (b) (4) is not wrong but it creates unnecessary confusion. I am in opinion that we can follow our more conventional approach as the starting point i.e. we can set a specification of NLT [REDACTED] (b) (4) % for the last time point. Now to accommodate Acceptance Table 1 in USP Chapter 724, we can put it in range form i.e. [REDACTED] (b) (4) %. We can also tell the firm that we are establishing range as per USP Chapter 724.

After looking at the data, I agree with the following specifications:

1 hr: [REDACTED] (b) (4)
2 hr: [REDACTED]
4 hr: [REDACTED]
9 hr: [REDACTED]
24 hr: [REDACTED] (b) (4)

Please let me know if you need any clarification/information.

Thank you

Om

From: Stier, Ethan
Sent: Wednesday, September 18, 2013 6:42 PM
To: Anand, Om; Mahadevan, Chitra
Subject:

Hi Om

Can you double check the specification for this? Specifically the fact that it's greater than [REDACTED] (b) (4) %? Y'm assuming it has to do with the fact that there is more drug in the dosage form then the label amount that will be delivered?

Summary of firms response

The firm accepted the specifications at 1, 2, 4, and 9 hour time points. The firm did not acknowledge the DB recommended specification at the 24 hour time point and requested that the DB revise the 24 hour time point specification to NLT (b) (4)% with no upper limit.

3.2 Item 2

Hi, Chandra:

Based on discussion with Ethan and Om, we came to a conclusion to adopt Om's recommended specifications:

Specifications:

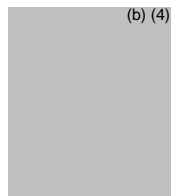
1 hour:

2 hours:

4 hours:

9 hours:

24 hours:



Would you please revise the review accordingly and insert the e-mail?

Thank you so much!

Xiaojian

From: Anand, Om

Sent: Tuesday, December 10, 2013 6:59 AM

To: Jiang, Xiaojian

Cc: Anand, Om; Stier, Ethan

Subject: RE: rivastigmine TDS dissolution specification, 204403

Xiaojian:

A few observations:

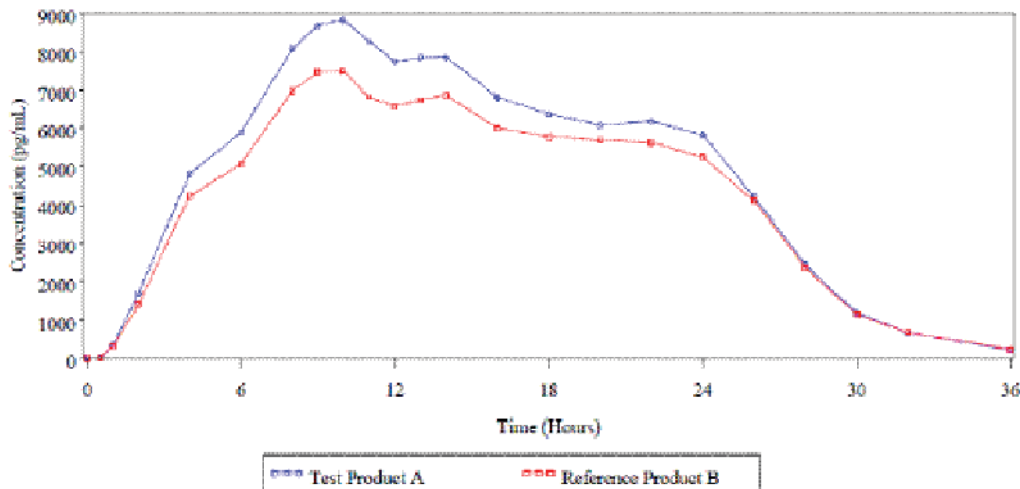
1. The BE study is a borderline study w.r.t. both Cmax and AUC.

AUC _{0-t} (pg-hr/mL)	12.004	11.877	163464.95	143876.95	113.61	(106.60, 121.09)
AUC _{0-inf} (pg-hr/mL)	12.010	11.883	164334.80	144824.77	113.47	(106.50, 120.90)
C _{max} (pg/mL)	9.112	8.971	9067.37	7869.17	115.23	(107.05, 124.02)

*Geometric means are based on the exponential of LSM of ln-transformed values.

- There is no direct in vivo relation to the in vitro performances. Please note that the in vitro release of the test product at 4 hours is approximately $\frac{(b)}{(4)}\%$ and that of reference is approximately $\frac{(b)}{(4)}\%$ i.e. RLD is 13%[>] than the test. However, the figure below shows that from 4-6 hours the plasma levels of the test product are above the reference. This also indicates that the test and reference product release mechanisms are different and it is not the best idea to completely follow the RLD style specifications. Also, the test batch should perform consistently as the bio-batch.

Figure 11.4.1 Mean Plasma Concentration (0 – 36 hours) for Rivastigmine (N = 27)



- As per information provided by you the test is designed to be 1.5 mg/cm² where as the RLD is designed to be 1.8 mg/cm² i.e. even though initially there is low concentration gradient from the test, at 4 hour we can see the in vivo release is much higher this indicates at two potential differences i.e. a. the test is releasing faster on skin and b.) formulation differences.
- The potency of the bio-batch of the test product is $\frac{(b)}{(4)}\%$. Please note that with increase in potency (to $\frac{(b)}{(4)}\%$) of the batches there is no significant affect on in vitro dissolution until 4 hours. However, only 9 hours and 24 hours capture these differences. There is no data to show the affect of these differences on bio, however in my opinion, the amount of drug available for absorption in between the patch and the skin can affect the bioavailability and hence BE, more so since this is a borderline product. The question is, how can the batches which are

releasing approximately (b) (4)% more than the bio-batch (at 24 hours) can be deemed bioequivalent to the bio-batch. Therefore, the specifications should be based on the bio-batch data only.

- 5 Please also note that with potency of (b) (4) % the bio-batch is releasing from (b) (4)% at 24 hours i.e. 5 to 14 % less than the mean assay, where as the new batches are releasing similar to the mean assay (mean dissolution of (b) (4)% assay respectively). Further, the firm is proposing the assay limit from (b) (4) (b) (4)% and content uniformity limit from (b) (4)%. I am not sure about the rationale behind these limits, more so since this is a borderline study.

Based on above observations, I am in opinion that the 9 hour and 24 hour time points are very important. The 24-hour time point release demonstrates that with change in assay, there is change in the dissolution and therefore we should keep this way. By changing it to NLT style, we miss the important information and control.

I am also in opinion that the Division of Chemistry should be consulted to discuss the limits of the assay and the content uniformity. If the assay limit of (b) (4)% is accepted then, based on bio-batch data, I recommend the following specifications:

Specifications:

1 hour:

2 hours:

4 hours:

9 hours:

24 hours:

(b) (4)

I am further in opinion that if the assay's upper limit is reduced to (b) (4)% then the 24 hour specifications should be reduced to (b) (4)%.

Please let me know if you have any further questions or need further discussion.

Thank you

Om

From: Jiang, Xiaojian

Sent: Monday, December 09, 2013 11:47 PM

To: Anand, Om

Cc: Stier, Ethan

Subject: rivastigmine TDS dissolution specification, 204403

Hi, Om:

I provided my proposal in the order of my preference and data as follows. Please let me know which option that you like.

Proposal:

I think firm's request is reasonable (please see below).

Option 1): remove specification at 24 hrs: a) the drug release in vivo is only 66% of the label claim b) the RLD specification is covering (b) (4)% at 7 hrs, c) at 9 hr, (b) (4)% in covered for the test product.

Option 2) recommend NLT (b) (4)% as we usually do for ER product. We can set up level 2 and level 3 specifications similarly as ranges.

Level 1: 6 patches are tested and each patch complies with the specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4)
Level 2: 6 additional patches are tested and the mean of 12 patches (Level 1 + Level 2) must comply with the Level 1 specification above and no patch is allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4)
Level 3: 12 additional patches are tested and the mean of 24 patches (Level 1 + Level 2 + Level 3) must comply with the above mentioned Level 1 specification. Maximum of two patches are allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4) and no patch is allowed to be outside of the following specification: 1 h: (b) (4) 4 h: (b) (4) 24 h: (b) (4)

Option 3) recommend (b) (4)%, I do not like this also.

Background:

We recommended the following specifications:

Specifications:

1 hour: (b) (4)
2 hours: (b) (4)
4 hours: (b) (4)
9 hours: (b) (4)

24 hours: (b) (4) %

The firm requested two times to change specification at 24 hrs to NLT (b) (4) %. The reason is that when the potency of the drug is above 100%, the % release at 24 hours exceed (b) (4) % (see the below data):

Assay (b) (4) %

N=12	1 h	2h	4h	9h	24 h
Mean [%J]	22.81	38.82	62.15	89.86	104.39
Min[%]	(b) (4)				
Max[%]					

Assay 111.0 %

N=6	1 h	2h	4h	9h	24 h
Mean [%J]	22.25	38.30	62.20	93.19	111.20
Min[%]	(b) (4)				
Max[%]					

Original data for the test are as follows:

0	1	2	4	7	9	12	24

Mean	0	23.53	38.01	57.69	73.72	79.59	84.64	90.60
Range	(b) (4)							
%CV	-	3.09	1.72	1.68	1.82	2.07	2.03	1.58

The RLD specification is :

2hr: (b) (4)
 4 hr
 7hr:

The original data for the reference:

Mean	0	40.10	56.34	69.83	78.10	81.04	84.06	89.64
Range	(b) (4)							
%CV	-	0.69	0.80	0.86	0.90	0.92	0.98	1.05

The content in the dosage units is greater than the actual dose per 24 hrs:

Dose (mg/24hr)	Test product		Reference product	
	Size (cm ²)	Rivastigmine Content (mg)	Size (cm ²)	Rivastigmine Content (mg)
4.6	4.6	6.9	5	9
9.5	9.2	13.8	10	18

The dissolution was

based on the label claim (1.5 mg/cm²). Only (b) (4)% of drug penetrate the skin over the 24 hrs. As stated in OCP review of the RLD, *“The in vitro release rate in 7 hours exceeds the in vivo delivery rate observed in 24 hours. From this argument, it can be concluded that the rates of drug dissolution in the in-vitro release test are not comparable to rates of in-vivo dermal absorption. Therefore, in vitro dissolution in this case is a quality control test.”*

3.3 Item 3

From: Jiang, Xiaojian
Sent: Wednesday, October 01, 2014 1:12 PM
To: Nair, Anil K; Raofi, Saeid; Stier, Ethan
Cc: Zhang, Hongling; Nhu, Duong T (Diane); Babaa, Nabeel
Subject: FW: rivastigmin 204403

Please see (b) (4) for example.
 You can send me the review vial e-mail.
 I will ask Nabeel or Diane to load it in GDRP as memorandum to file.

Thanks,
 Xiaojian

From: Zhang, Hongling
Sent: Tuesday, September 30, 2014 9:50 AM
To: Jiang, Xiaojian

Cc: Zhang, Hongling
Subject: rivastigmin 204403

Hi Xiaojian,

For this drug product, there is no relationship between the in vitro dissolution testing and in vivo drug delivery, shown as: 1) the innovator's study (the OCP reviewer of the NDA stated that *"The in vitro release rate in 7 hours exceeds the in vivo delivery rate observed in 24 hours. From this argument, it can be concluded that the rates of drug dissolution in the in-vitro release test are not comparable to rates of in-vivo dermal absorption.*

Therefore, in vitro dissolution in this case is a quality control test."; 2) ANDA (b) (4), in which the proposed test product (b) (4)

Based on these findings, the dissolution specifications should be set without the consideration of the results of the in vivo study.

Per the chemistry review dated 3/7/2014, the specification for both RLD product and the test product is (b) (4)% of label claim, which was found acceptable. Therefore, there should be no concerns for the overage of the test product. For RLD product, the dissolution specification for the last time point is 7hrs (b) (4), which does not have control for 24 hour drug release.

Based on above information, in my opinion, we can adopt the firm's proposed specification of NLT (b) (4)% in 24 hours.

Please note that for the chemistry review issued an major deficiency for the application (b) (4)

The chemistry review of the firm's justification is not completed. There is high possibility that the firm needs to reformulate the test product.

These are my thoughts. Please let me know if you have any questions.

Thanks,

Hongling

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/s/

DUONG NHU
10/09/2014

Lemley, Carrie

From: Lemley, Carrie
Sent: Friday, September 05, 2014 12:53 PM
To: Potter, Andrew; Edward, Hany; Nhu, Duong T (Diane)
Subject: RE: ANDA 204403/ Alvogen/ Rivastigmine Transdermal System/ Meeting Request

3. Package Insert and Patient Information Leaflet

We note that revised package insert labeling has been recently approved for the reference listed drug, Exelon® Patch by Novartis (NDA 22-083/S-0 19; approved June 27,2013) and these revisions are protected by exclusivity. Please address how you will certify regarding this recent update.

Alvogen Question:

Alvogen asks whether it will suffice to submit an amended exclusivity statement to the ANDA, along with labeling amended in which there is a (b) (4)

FDA Response: A labeling amendment with MOU certification and the protected information carved out would suffice.

From: Potter, Andrew
Sent: Friday, September 05, 2014 12:38 PM
To: Edward, Hany; Nhu, Duong T (Diane); Lemley, Carrie
Subject: ANDA 204403/ Alvogen/ Rivastigmine Transdermal System/ Meeting Request

Team,

All disciplines have agreed to a written response for this meeting request. Could you please have the responses loaded into DARRTS by COB September 19, 2014? If you will require additional time please let me know.

Thank you,
Andrew

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/s/

CARRIE L LEMLEY
09/08/2014



ANDA 204403

**MEETING REQUEST GRANTED
WRITTEN RESPONSES ONLY**

Alvogen Pine Brook, Inc.
Attention: Patricia Jaworski
Vice President, Regulatory Affairs
10 Bloomfield Avenue
Pine Brook, NJ 07058

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 12, 2012, received June 12, 2012, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Rivastigmine Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr and 13.3 mg/24 hr.

We also refer to your August 11, 2014, correspondence requesting a Post Complete Response Teleconference Meeting to discuss deficiencies noted in the Complete Response Letter dated July 25, 2014.

We have determined that written responses to your questions would be the most appropriate means for responding to the meeting request. Therefore, a teleconference will not be scheduled. Our goal date for providing our written responses is October 25, 2014.

If you have any questions, call Andrew Potter, Regulatory Project Manager at (240) 402-9266.

Sincerely,

{See appended electronic signature page}

Andrew Potter
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

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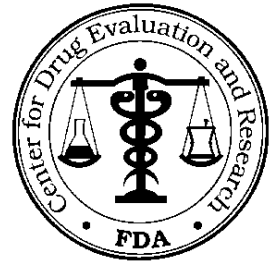
/s/

THANH M ANDREWS
08/28/2014

COMPLETE RESPONSE

ANDA 204403

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



TO: Alvogen Pine Brook, Inc.

TEL: [REDACTED] (b) (6)

ATTN: Jasmine Shah

FAX: 973-201-1086

FROM: Surjit Basi

FDA CONTACT PHONE: 240-402-8892

Dear Madam:

This facsimile is in reference to your abbreviated new drug application, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

We have completed the review and have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (____ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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ANDA 204403

COMPLETE RESPONSE

Alvogen Pine Brook, Inc.
Attention: Jasmine Shah
Vice President, Regulatory and Medical Affairs
10 Bloomfield Avenue, Building B
Pine Brook, NJ 07058

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 12, 2012, received June 12, 2012, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Rivastigmine Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr.

We acknowledge receipt of your amendments dated October, 19, 2012; and January 3, January 22, April 11, April 22, May 2, June 12, June 20, July 30, September 20, November 11, and December 27, 2013.

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

PRODUCT QUALITY

A. Major Deficiencies

- 1.
- 2.
- 3.



B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide any additional stability data that is available for the drug product.
2.  (b) (4)
3. For each product strength, please provide Rivastigmine Transdermal System samples of the RLD and applicant's drug product.
4. Please update the Master Batch Records to include changes resulting from this letter.

The establishments referenced in the application should be in compliance with cGMP at the time of approval.

BIOEQUIVALENCE

The Division of Bioequivalence (DB) II has completed its review and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

DISSOLUTION

The Division of Bioequivalence II (DBII) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The following deficiency has been identified:

 (b) (4)

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications:

1 hour:  (b) (4)
2 hours: 
4 hours: 
9 hours: 
24 hours: 

Please acknowledge the above recommended dissolution method and specifications.

CLINICAL

The Division of Clinical Review has completed its review of your skin irritation, sensitization, and adhesion data based on the information available and has no further questions at this time. The Division of Clinical Review recommends that the skin irritation, sensitization, and adhesion data submitted to ANDA 204403 are adequate to support approval of the application based on information available.

Please note that the clinical bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

LABELING

Labeling Deficiencies determined on September 17, 2013 based on your submission dated June 12, 2012 and January 22, 2013:

 (b) (4)



a. Place the NDC # and Rx only statement at the top left and right of the label

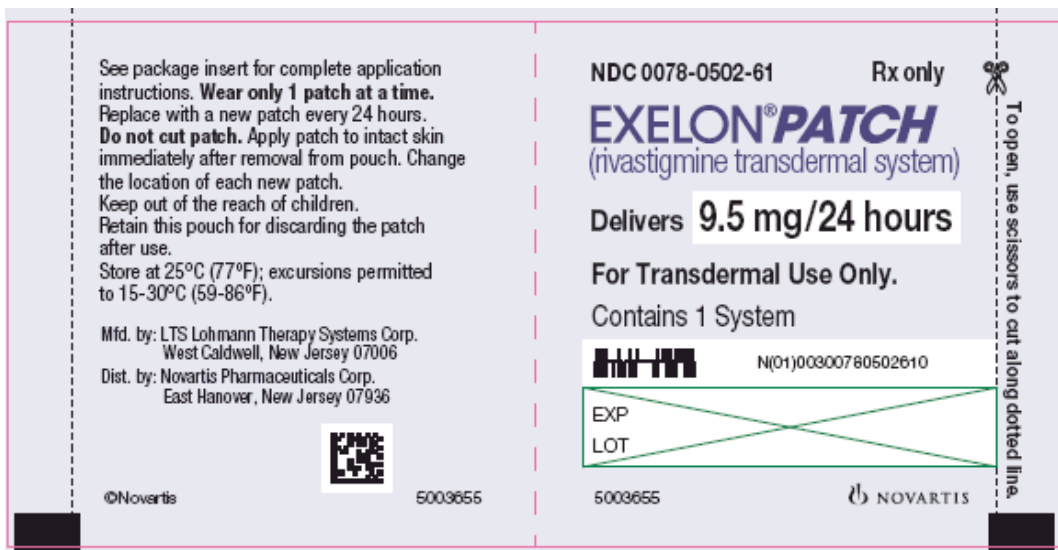
b. Delete from the label:



c. Include the statement “For Transdermal Use Only” on the front panel as well as the side panel to be in accord with the RLD.

2. Individual Pouch -

Please utilize this sample of the RLD pouch as guidance for the layout of your proposed labels. (Note the following recommendations pertain to both proposed strengths).



- a. See comment 1(c.) above
- b. We note that you did not submit a pouch that included instructions and product information on the back side for the 4.6 mg/24 hr and the 9.5 mg/24 hr strength patches. Please revise and submit to be in accord with the reference listed drug.

3. Package Insert and Patient Information Leaflet

We note that revised package insert labeling has been recently approved for the reference listed drug, Exelon® Patch by Novartis (NDA 22-083/S-019; approved June 27, 2013) and these revisions are protected by exclusivity. Please address how you will certify regarding this recent update.

Patent and Exclusivity Search Results from query on Appl No 022083 Product 005 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N022083	005	5602176	Feb 11, 2014	Y	Y	U - 322	
N022083	005	6316023	Jan 8, 2019		Y		
N022083	005	6335031	Jan 8, 2019		Y		

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N022083	005	NPP	Jun 27, 2016
N022083	005	NS	Aug 31, 2015

Additional information:

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug's labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

FACILITY INSPECTIONS

Office of Compliance has no further questions at this time. The compliance status of each facility named in the application may be re-evaluated upon re-submission.

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
CHEMISTRY/DISSOLUTION/LABELING**

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 ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

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

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees

when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, call Surjit Basi, Regulatory Project Manager, at (240) 402-8892.

Sincerely yours,

{See appended electronic signature page}

Denise P. Toyer McKan, Pharm.D.
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

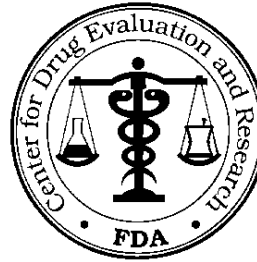
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/s/

WILLIAM P RICKMAN
07/25/2014

FDA FAX

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



TO: ALVOGEN INC

TEL: [REDACTED] (b) (6)

ATTN: Jasmine Shah

FAX: 973-201-1086

This facsimile is in reference to your abbreviated new drug application(s), submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Pages (including cover): 4

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If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

DATE: 2/4/2014

TO: ALVOGEN INC

ATTN: Jasmine Shah

E-Mail: jasmine.shah@alvogen.com

FAX: 973-201-1086

RE: Update summary of filed and pending original ANDA(s)

Dear Sir or Madam:

The Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research, Food and Drug Administration (FDA), is providing you with this one-time communication on the status of your filed and pending original abbreviated new drug application(s) (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act. OGD is providing these updates as an interim measure to help applicants assess the status of their current submissions as we transition towards predictable goal times pursuant to the Generic Drug User Fee Amendments of 2012 (GDUFA).

Your status update is limited to available review information as of January 29, 2014. Any additional information regarding your ANDA collected after this date is neither considered nor provided. Furthermore, your ANDA status is subsequently subject to revision pending additional information or concerns raised by any of the discipline reviews (bioequivalence, clinical, chemistry, microbiology, labeling, facility), other unforeseen legal, scientific or regulatory issues, or inspectional results, which can also impact the status or ability to issue a complete response. Any applicable fees can also affect the status of your ANDA.

OGD is providing your ANDA status update in the attached chart with a list of applicable acronyms. The chart only contains current information regarding discipline review and does not forecast if and when OGD will issue a complete response, tentative approval, or final approval letter.

Please do not respond to this communication by asking FDA or your Regulatory Project Manager for additional or more detailed information. This is a one-time communication intended to assist you to ascertain the current status of submissions. It is not feasible for us to respond to a high volume of follow up inquiries.

Sincerely yours,

CAPT Aaron W. Sigler, USPHS
Chief, Review Support Branch

ANDA	DRUG NAME	CHEM	BIO	MICRO	LABEL	CLINICAL	FACILITY
203924	PRIMAQUINE PHOSPHATE	AQ	AQ	NA	AQ	NA	AC
(b) (4)							
204737	PYRIDOSTIGMINE BROMIDE	IQ	IQ	NA	IQ	NA	AC
205055	NATEGLINIDE	NR	NR	NA	UR	NA	AC
204403	RIVASTIGMINE	UR	UR	NA	IQ	IQ	PN

CHART ACRONYMS

Column Headings

ANDA	- The application number for your Abbreviated New Drug Application
DRUG NAME	- The official filed name of the drug associated with the ANDA number
CHEM	- Product Quality Chemistry Review
BIO	- Bioequivalence Review, typically including OSI, if applicable
MICRO	- Microbiology Review
LABEL	- Labeling Review
CLINICAL	- Clinical Review
FACILITY	- Overall Facility inspections summary. All facilities must be acceptable at the time of 29 JAN 14 in order to warrant an adequate notation. If one of more facility is not acceptable then the FACILITY column will be marked as such. OSI information is not considered.

Discipline Notations

- IQ - Inadequate. This particular discipline is currently found to be inadequate.
- AQ - Adequate. This particular discipline was found to be adequate when the information was gathered for this communication.
- UR - Under Review. This particular discipline is currently assigned OR under review with the discipline team.
- NR - Not Reviewed. This particular discipline is either currently not under review or assigned.
- NA - Not applicable. This particular discipline is not required for the approval of this ANDA.

Facility Notations

- PN - Pending, i.e., one or more facilities have been inspected and are pending an outcome.
- AC - All facilities are acceptable at the time of this publication.

*Please note that you may receive your updates in multiple communications over time, based on the number of ANDAs pending in OGD.

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/s/

AARON W SIGLER
02/07/2014

MEMORANDUM

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

DATE: January 09, 2014

TO: Director, Investigations Branch
Kansas District Office
11630 W.80th Street
Lenexa, KS 66214

FROM: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: **FY 2014, CDER ANDA, High Priority Data Validation 'For Cause' Inspection**, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: ANDA 204-403
DRUG: Rivastigmine transdermal system
4.6 mg/24 hr, 9.5 mg/24 hr, 13.3 mg/24 hr
SPONSOR: Alvogen Pine Brook, Inc., Pine Brook, NJ

This memo requests that you arrange a 'For Cause' inspection of the clinical portion of the following irritation and sensitization evaluation study.

Once you identify an ORA investigator, please contact the DBGLPC point of contact (POC) listed at the end of this assignment memo. Background materials will be available in ECMS under the ORA folder. **The inspection should be completed prior to April 30, 2014**

Do not reveal information about the applicant/sponsor, application number, study to be inspected, drug name, or the study investigators to the site prior to the start of the inspection. The site will receive this information during the inspection opening meeting.

The inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

At the completion of the clinical inspection, please send a scanned copy of the completed section A of this memo to the DBGLPC POC.

1. Study number: C10-1870 (R10-1318, S11-0069)

Study Title: "A multiple site study to evaluate the irritation and sensitization potential of repeat applications of rivastigmine 4.6 mg/24 hours patch (transdermal system) versus Exelon 4.6 mg/24 hours patch (rivastigmine transdermal system) in normal healthy volunteers"

Clinical Site: *Cetero Research - St. Charles
400 Fountain Lakes Blvd.
St. Charles, MO 63301

Investigators: James C. Freeman, M.D.

*Please note that the firm was reorganized (Chapter 11 bankruptcy) under the name PRACS Institute and subsequently liquidated (Chapter 7 bankruptcy). The firm is currently out of business and the site is closed. The study documents and reserve samples will be available for audit at a future date, under arrangements being made by the bankruptcy court's appointed receiver. OSI will notify the Kansas District Office when study documents are available.

Also please note the review division has requested a 'For Cause' inspection based on the OAI outcome of a previous inspection conducted in November 2012. The previous inspection was classified OAI because of number of deficiencies, particularly due to lack of adequate study records available at the time of FDA inspection.

SECTION A - CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

During the clinical site inspection, please:

- Confirm the informed consent forms and study records for 100% of subjects enrolled at the site.

- Compare the study report in the ANDA submission to the original documents at the site.
- Check for under-reporting of adverse events (AEs).
- Check for evidence of inaccuracy in the electronic data capture system.
- Check reports for the subjects audited.
 - o Number of subject records reviewed during the inspection:_____
 - o Number of subjects screened at the site:_____
 - o Number of subjects enrolled at the site:_____
 - o Number of subjects completing the study:_____
- Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.
- Confirm that site personnel followed SOPs during study conduct.
- Examine correspondence files for any applicant or monitor-requested changes to study data or reports.
- Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- Other comments:

Additional instructions to the ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to commencement of the inspection. Therefore, we request that the DBGLPC POC be contacted for any further instructions, inspection related questions or clarifications before the inspection and

Page 4 - BIMO Assignment, ANDA 204-403, Rivastigmine transdermal system, sponsored by Alvogen Pine Brook, Inc.

also regarding any data anomalies or questions noted during review of study records on site.

If you issue Form FDA 483, please forward a copy to the DBGLPC POC. If it appears that the observations may warrant an OAI classification, notify the DBGLPC POC as soon as possible.

Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to the DBGLPC POC.

DBGLPC POC: Jyoti Patel, Ph.D.
Pharmacologist
Office of Scientific Investigations
Tel: 1-301-796-4617
Fax: 1-301-847-8748
E-mail: jyoti.patel@fda.hhs.gov

DARRTS cc:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Bonapace/Haidar/Choi/Patel/Dejernett
CDER/OPS/OGD/DCR/Peters/Patel

Email cc:
KAN-DO/ORAKANBIMO@fda.hhs.gov/DIB-Bromley/BIMO-
Lopicka/Bous/Kuchenthal/Kanion

Draft: JBP 01/08/2014
Edit: YMC 01/09/2014; SHH 01/09/2014

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/ Clinical
Sites/Cetero Research-St. Charles.

OSI file #: BE 6519; assignment file name: bio204403

FACTS: 8742033

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/s/

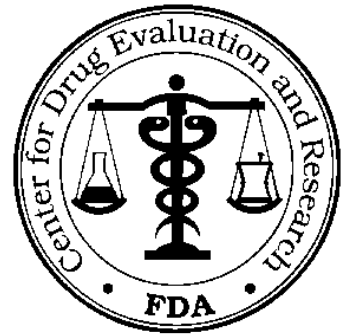
JYOTI B PATEL
01/09/2014

SAM H HAIDAR
01/09/2014

EASILY CORRECTABLE DEFICIENCY EMAIL

ANDA 204403

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



APPLICANT: Alvogen Pine Brook, Inc.

TEL [REDACTED] (b) (6)

ATTN: Mr. Jasmine Shah

FAX: 973-201-1086

FROM: Esther Chuh

FDA CONTACT PHONE: (240) 276-8573

Dear Sir:

This communication is in reference to your abbreviated new drug application (ANDA) dated August 24, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Rivastigmine Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies with an "*EASILY CORRECTABLE DEFICIENCY AMENDMENT*" within ten (10) business days.

If you do not submit a complete response within ten (10) business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments. In addition, please notify the Regulatory Project Manager.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review. Please notify the Regulatory Project Manager when your amendment has been submitted.

If you have questions regarding these deficiencies please contact the Regulatory Project Manager, Esther Chuh at (240) 276-9663.

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BIOEQUIVALENCE

Please submit the Certificate of Analysis (COA) for the Reference Listed Drug, Exelon Patch, 9.5 mg/24 hours (Lot #1401B) used in the bioequivalence study # R10-1307. Please submit this information electronically to the OGD Document Room no later than 5PM on Friday, January 10, 2014.

APPEARS THIS WAY ON
ORIGINAL

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/s/

KULDEEP R DHARIWAL
12/26/2013

November 1, 2013

The following ANDAs have been removed from the list attached to the below document because they do not meet the criteria for this expedited granting. They either: (a) did not secure a Tentative Approval or Approval (TA/AP) by their 30/40 month date, or (b) converted from P-IV to P-III.

(b) (4)

ANDA 201963 –No TA/AP on or before 10/1/13

ANDA 202136 – TA'd on 10/21/13

ANDA 202073 – No TA/AP on or before 10/23/13

ANDA 202118 – No TA/AP on or before 10/23/13

ANDA 202103 – No TA/AP on or before 10/28/13

ANDA 204009 – firm was a FTF but converted PIV's to PIII

OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA#/SUPPLEMENT#: MULTIPLE ANDAs
 DRUG: See list below of pre-MMA
 Expedite Candidates

APPLICANT: MULTIPLE APPLICANTS
 DATE OF SUBMISSION:VARIOUS

The Office of Generic Drugs may grant expedited review status to either an Original or Supplemental abbreviated new drug application for the following reasons (MaPP 5240.1, & MaPP 5240.3). At least one of the criteria must be met to receive Expedited Review Status:

1. PUBLIC HEALTH NEED. Events that affect the availability of a drug for which there is no alternative
2. EXTRAORDINARY HARDSHIP ON THE APPLICANT.
 - a) Catastrophic events such as explosion, fire storms damage.
 - b) Events that could not have been reasonably foreseen and for which the applicant could not plan. Examples include:
 - ◆ Abrupt discontinuation of supply of active ingredient, packaging material, or container closure; and
 - ◆ Relocation of a facility or change in an existing facility because of a catastrophic event(see item 2.a)
3. AGENCY NEED.
 - a) Matters regarding the government's drug purchase program, upon request from the appropriate FDA office.
 - b) Federal or state legal/regulatory actions, including mandated formation changes or labeling changes if it is in the Agency's best interest.
 - c) Expiration-date extension or packaging change when the drug product is the subject of a government contract award.
 - d) Request for approval of a strength that was previously tentatively approved (To be used in those cases where 180-day generic drug exclusivity prevented full approval of all strengths).
 - e) MaPP 5240.3 conditions.

RECOMMENDATIONS:

DISCIPLINE	STATUS	SIGNATURE/DATE
Team Project Manager (PM must Endorse)	Grant ☒ Deny ☐	
Chemistry Team Leader (sign as needed)	Grant ☒ Deny ☐	
Micro Team Leader (sign as needed)	Grant ☒ Deny ☐	
Labeling Team Leader (sign as needed)	Grant ☒ Deny ☐	
Chem. Div./Deputy Director (DO must Endorse)	Grant ☒ Deny ☐	
Office Director/Deputy Director (email concurrence) (Original ANDAs)	Grant ☒ Deny ☐	

RETURN TO PROJECT MANAGER CHEMISTRY TEAM: SELECT TEAM #

a) When expedited review is denied, notify the applicant by telephone

ENTER FORM INTO DFS

DATE 10/18/13

Paste Email Copy Below:

On 10/8/13 OGD Leadership decided to grant expedite review status to the following listed pre-GDUFA (Submitted prior to 10/1/12) Paragraph IV applications that were submitted on the first day that any valid Paragraph IV application for the drug in question may be submitted. This action is being taken to ensure consistency in review priority in order to for timely review and FDA action on these ANDAs. These are ANDA if submitted in the year 1 and 2 cohorts, FDA would expedite review under the GDUFA Commitment provided in the Generic Drug User Fee Act Program Performance Goals and Procedures (<http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf>)

201963	Actavis	Pramipexole Dihydrochloride	Extended- release Tablets	0.375 mg, 0.75 mg, 1.5 mg, 3 mg and 4.5 mg	Mirapex ER	6/1/2010	10/1/2013

202118	Teva	Darunavir Ethanolate	Tablets	75 mg, 150 mg, 300 mg, 400 mg and 600 mg	Prezista	6/23/2010	10/23/2013
202136	Mylan	Darunavir Ethanolate	Tablets	75 mg, 150 mg, 300 mg, 400 mg and 600 mg	Prezista	6/23/2010	10/23/2013
202103	Apotex	Dasatinib	Tablets	20 mg, 50 mg, 70 mg and 100 mg	Sprycel	6/28/2010	10/28/2013
202090	Roxance	Sodium Oxybate	Oral Solution	500 mg/mL	Xyrem	7/8/2010	11/8/2013
202144	Watson	Hydromorphone Hydrochloride	Extended- release Tablets	16 mg	Exlago	8/2/2010	12/2/2013
202294	Handa	Dexlansoprazole	Delayed- release Capsules	60 mg	Dexilant	8/25/2010	12/25/2013
201676	Zydus	Sirolimus	Tablets	0.5 mg	Rapamune	8/25/2010	12/25/2013
200744	Nycomed	Tacrolimus	Ointment	0.10%	Protopic	9/9/2010	1/9/2014
202337	Mylan	Doxepin Hydrochloride	Tablets	3 mg and 6 mg	Silenor	9/16/2010	1/16/2014

91182	Statson	Glycopyrrolate	Tablets	2 mg	Robinul Forte	10/12/2010	2/12/2014
(b) (4)							
202487	Teva	Sitagliptin Phosphate	Tablets	25 mg, 50 mg and 100 mg	Januvia	10/18/2010	2/18/2014
202425	Apotex	Sitagliptin Phosphate	Tablets	25 mg, 50 mg and 100 mg	Januvia	10/18/2010	2/18/2014
(b) (4)							
202426	Apotex	Sitagliptin Phosphate and Metformin Hydrochloride	Tablets	50 mg/500 mg and 50 mg/1000 mg	Janumet	10/18/2010	2/18/2014
(b) (4)							
202349	Watson	Estradiol Valerate and Dienogest	Tablets	3 mg;2 mg/2 mg;2 mg/3 mg and 1 mg	Natazia	10/22/2010	2/22/2014
202509	Anchen	Dutasteride and Tamsulosin Hydrochloride	Capsules	0.5 mg/0.4 mg	Jalyn	10/26/2010	2/26/2014
91118	Ranbaxy	Minocycline Hydrochloride	Extended-release Tablet	80 mg	Solodyn	10/27/2010	2/27/2014
(b) (4)							
202511	Novel Labs	Sodium Sulfate, Potassium Sulfate and Magnesium Sulfate	Oral Solution	17.5 g/3.13 g/1.6 g	Suprep Bowel Prep Kit	11/8/2010	3/8/2014

200744	Fougera	Tacrolimus	Ointment	0.03%	Protopic	11/22/2010	3/22/2014
200652	Roxane	Alosetron Hydrochloride	Tablets	0.5 mg and 1 mg	Lotronex	12/2/2010	4/2/2014
202731	Teva	Dexmethylphenidate Hydrochloride	Extended-release Capsules	40 mg	Focalin XR	12/20/2010	4/20/2014
202573	Roxane	Ritonavir	Tablets	100 mg	Norvir	12/21/2010	4/21/2014

(b) (4)

202827	Roxane	Lisdexamfetamine Dimesylate	Capsules	20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg	Vyvanse	2/23/2011	6/23/2014
202830	Amneal	Lisdexamfetamine Dimesylate	Capsules	20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg	Vyvanse	2/23/2011	6/23/2014
202835	Mylan	Lisdexamfetamine Dimesylate	Capsules	20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg	Vyvanse	2/23/2011	6/23/2014
202836	Sandoz	Lisdexamfetamine Dimesylate	Capsules	20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg	Vyvanse	2/23/2011	6/23/2014

(b) (4)

202308	Sandoz	Azithromycin	Ophthalmic Solution	1%	Azasite	3/3/2011	7/3/2014
202993	Par	Dextromethorphan Hydrobromide and Quinidine Sulfate	Capsules	20 mg/10 mg	Nuedexta	3/7/2011	7/7/2014
202931	Mylan	Frovatriptan	Tablets	2.5 mg	Frova	3/9/2011	7/9/2014

		Succinate					
203007	Natco	Lapatinib Ditosylate	Tablets	250 mg	Tykerb	3/14/2011	7/14/2014
(b) (4)							
202912	Lupin	Abacavir Sulfate, Lamivudine and Zidovudine	Tablets	300 mg/150 mg/300 mg	Trizivir	3/22/2011	7/22/2014
203005	Alkem	Mycophenolic Mofetil	For Oral Suspension	200 mg/mL	Cellcept	3/25/2011	7/25/2014
(b) (4)							
203039	Teva	Clozapine	Orally Disintegrating Tablets	150 mg and 200 mg	Fazaclo	4/8/2011	8/8/2014
203139	TWI	Megestrol Acetate	Oral Suspension	125 mg/mL	Megace ES	4/27/2011	8/27/2014
(b) (4)							
202521	Sandoz	Palonosetron Hydrochloride	Injection	0.05 mg/mL, 1.5 mL and 5 mL vials	Aloxi	5/27/2011	9/27/2014
(b) (4)							
203286	Zydus	Mesalamine	Delayed- release Tablets	800 mg	Asacol HD	7/13/2011	11/13/2014
(b) (4)							
202206	Anchen	Pramipexole Dihydrochloride	Extended- release Tablets	2.25 mg and 3.75 mg	Mirapex ER	7/26/2011	11/26/2014

203371	Famy Care	Norethindrone and Ethinyl Estradiol and Ferrous Fumarate	Chewable Tablets	0.8 mg/0.025 mg and 75 mg	Generess Fe	8/5/2011	12/5/2014
203347	Hetero	Maraviroc	Tablets	150 mg and 300 mg	Selzentry	8/8/2011	12/8/2014
203560	Actavis	Deferasirox	Tablets	125 mg, 250 mg, and 500 mg	Exjade	10/28/2011	2/28/2015
203611	Actavis	Gabapentin	Tablets	300 mg and 600 mg	Gralise	10/31/2011	3/3/2015
203564	Silarx	Lamivudine	Oral Solution	10 mg/mL	Epivir	11/22/2011	3/22/2015
203649	Sandoz	Treprostinil Sodium	Injection	10 mg/mL, 20 mL vial	Remodulin	12/2/2011	4/2/2015

(b) (4)

203741	Alkem	Nebivolol Hydrochloride	Tablets	2.5 mg, 5 mg, 10 mg, and 20 mg	Bystolic	12/19/2011	4/19/2015
203683	Watson	Nebivolol Hydrochloride	Tablets	2.5 mg, 5 mg, 10 mg, and 20 mg	Bystolic	12/19/2011	4/19/2015
203821	Glenmark	Nebivolol Hydrochloride	Tablets	2.5 mg, 5 mg, 10 mg, and 20 mg	Bystolic	12/19/2011	4/19/2015
203966	Torrent	Nebivolol Hydrochloride	Tablets	2.5 mg, 5 mg, 10 mg, and 20 mg	Bystolic	12/19/2011	4/19/2015
203828	Indchemie	Nebivolol Hydrochloride	Tablets	2.5 mg, 5 mg, 10 mg, and 20 mg	Bystolic	12/19/2011	4/19/2015

(b) (4)

203689	Watson	Vardenafil	Orally Disintegrating	10 mg	Staxyn	12/22/2011	4/22/2015

		Hydrochloride	Tablets				
(b) (4)							
203790	Actavis	Adapalene and Benzoyl Peroxide	Gel	0.1%/2.5%	Epiduo	12/30/2011	4/30/2015
(b) (4)							
204025	Accord	Fosaprepitant Dimeglumine	Injection	150 mg/vial	Emend	1/25/2012	5/25/2015
(b) (4)							
204029	Abon	Clofarabine	Injection	1 mg/mL, 20 mL vial	Clolar	2/23/2012	6/23/2015
(b) (4)							
204082	Roxane	Desvenlafaxine Succinate	Extended-release Tablets	50 mg and 100 mg	Pristiq	2/29/2012	6/29/2015
(b) (4)							
204065	Watson	Desvenlafaxine Succinate	Extended-release Tablets	50 mg and 100 mg	Pristiq	2/29/2012	6/29/2015
(b) (4)							
204083	Roxane	Desvenlafaxine Succinate	Extended-release Tablets	50 mg and 100 mg	Pristiq	2/29/2012	6/29/2015

204095	Mylan	Desvenlafaxine Succinate	Extended-release Tablets	50 mg and 100 mg	Pristiq	2/29/2012	6/29/2015
204003	Alembic	Desvenlafaxine Succinate	Extended-release Tablets	50 mg and 100 mg	Pristiq	2/29/2012	6/29/2015
204020	Zydus	Desvenlafaxine Succinate	Extended-release Tablets	50 mg and 100 mg	Pristiq	2/29/2012	6/29/2015
204009	Anchen	Desvenlafaxine Succinate	Extended-release Tablets	50 mg and 100 mg	Pristiq	2/29/2012	6/29/2015

(b) (4)

204028	Sandoz	Desvenlafaxine Succinate	Extended-release Tablets	50 mg and 100 mg	Pristiq	2/29/2012	6/29/2015
204079	Lupin	Moxifloxacin Hydrochloride	Ophthalmic Solution	0.5%	Moxeza	2/29/2012	6/29/2015

(b) (4)

204403	Alvogen	Rivastigmine	Transdermal System Extended-release	4.6 mg/24 hr and 9.4 mg/24 hr	Exelon Patch	6/12/2012	7/22/2015

(b) (4)

(b) (4)

204268	Perrigo	Testosterone	Gel	1.62%	Androgel	4/6/2012	8/6/2015

(b) (4)

204299	Novel Labs	Zolpidem Tartrate	Sublingual Tablets	1.75 mg and 3.5 mg	Intermezzo	4/10/2012	8/10/2015

(b) (4)

90694	Lupin	Duloxetine Hydrochloride	Delayed-release Capsules	40 mg	Cymbalta	5/10/2012	9/10/2015

(b) (4)

204438	Par	Glycopyrrolate	Oral Solution	1 mg/5 mL	Cuvposa	6/20/2012	*9/30/2015*

(b) (4)

203485	Accord	Pemetrexed Disodium	For Injection	1000 mg/vial	Alimta	6/27/2012	*9/30/2015*
202027	Apotex	Diclofenac Sodium	Topical Solution	1.5%	Pennsaid	7/11/2012	1/11/2015
204637	Glenmark	Azelaic Acid	Gel	15%	Finacea	7/27/2012	1/27/2015
204571	Watson	Testosterone	Gel	10 mg/actuation	Fortesta	8/14/2012	2/14/2015

202191	Novel Labs	Metoclopramide Hydrochloride	Orally Disintegrating Tablets	5 mg and 10 mg	Metozolv ODT	8/24/2010	12/24/2013	CR
(b) (4)								
202362	Mylan	Atovaquone and Proguanil Hydrochloride	Tablets	62.5 mg/25 mg	Malarone	9/14/2010	1/14/2014	CR
202327	Watson	Sitagliptin Phosphate	Tablets	25 mg, 50 mg and 100 mg	Januvia	10/18/2010	2/18/2014	CR
202365	Watson	Sitagliptin Phosphate and Metformin Hydrochloride	Tablets	50 mg/500 mg and 50 mg/1000 mg	Janumet	10/18/2010	2/18/2014	CR
(b) (4)								
202595	Natco	Oseltamivir Phosphate	Capsules	75 mg	Tamiflu	11/15/2010	3/15/2014	CR
(b) (4)								
202470	River's Edge	Desonide	Gel	0.05%	Desonate	12/1/2010	4/1/2014	CR
202564	Actavis	Clindamycin Phosphate and Tretinoin	Gel	1.2%/0.025%	Ziana	12/17/2010	4/17/2014	CR
(b) (4)								
202802	Actavis	Lisdexamfetamine Dimesylate	Capsules	20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg	Vyvanse	2/23/2011	6/23/2014	CR
(b) (4)								
203056	Sandoz	Bimatoprost	Ophthalmic Solution	0.01%	Lumigan	4/5/2011	8/5/2014	CR
203113	Lupin	Norethindrone Acetate and Ethinyl Estradiol / Ethinyl Estradiol and Ferrous Fumarate	Tablets	1 mg/0.01 mg, 0.01 mg and 75 mg	Lo Loestrin Fe	4/29/2011	8/29/2014	CR
203174	Banner	Bexarotene	Capsules	75 mg	Targretin	6/6/2011	10/6/2014	CR
203217	Teva	Risedronate Sodium	Delayed-release Tablets	35 mg	Atelvia	6/9/2011	10/9/2014	CR

203294	Aurobindo	Azithromycin	for Injection	500 mg/vial	Zithromax	6/17/2011	10/17/2014	CR
202159	Hikma	Hydromorphone Hydrochloride	Injection	2 mg/mL	Dilaudid	6/22/2011	10/22/2014	CR
202595	Natco	Oseltamivir Phosphate	Capsules	30 mg and 45 mg	Tamiflu	8/2/2011	12/2/2014	CR
203382	Sandoz	Maraviroc	Tablets	150 mg and 300 mg	Selzentry	8/8/2011	12/8/2014	CR
(b) (4)								
202842	Par	Dexmethylphenidate	Extended-release Capsules	35 mg	Focalin XR	9/29/2011	1/29/2015	CR
(b) (4)								
203563	Sandoz	Levoleucovorin Calcium	Injection	10 mg/mL, 17.5 mL vial and 25 mL vial	Fusilev	10/26/2011	2/26/2015	CR
203557	Sandoz	Piperacillin Sodium and Tazobactam Sodium	For Injection	12 g/1.5 g per vial (pharmacy bulk)	Zosyn	12/6/2011	4/6/2015	CR
202743	Perrigo	Azelastine Hydrochloride	Nasal Spray	205.5 mcg/spray	Astepro	12/15/2011	4/15/2015	CR
203659	Amerigen	Nebivolol Hydrochloride	Tablets	2.5 mg, 5 mg, 10 mg, and 20 mg	Bystolic	12/19/2011	4/19/2015	CR
204172	Lupin	Desvenlafaxine Succinate	Extended-release Tablets	50 mg and 100 mg	Pristiq	2/29/2012	6/29/2015	CR
204144	Anchen	Sitagliptin Phosphate and Metformin Hydrochloride	Extended-release Tablets	50 mg/500 mg and 50 mg/1000 mg	Janumet XR	3/16/2012	7/16/2015	CR

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/s/

ROBERT T GAINES
10/24/2013

ROBERT L WEST
10/24/2013
Deputy Director, Office of Generic Drugs

BIOEQUIVALENCE AMENDMENT

ANDA 204403

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810



APPLICANT: Alvogen Pine Brook, Inc.

TEL: [REDACTED] (b) (6)

ATTN: Jasmine Shah

FAX: (973) 201-1086

FROM: Chitra Mahadevan

FDA CONTACT PHONE: (240) 402-3880

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on June 12, 2012, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Rivastigmine Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr.

Reference is also made to your amendment dated June 20, 2013.

The Division of Bioequivalence II has completed its review of the submissions referenced above and has identified deficiencies which are presented on the attached ___ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

Bioequivalence Dissolution Acknowledgement

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response. Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket.** Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence II, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

BIOEQUIVALENCE DEFICIENCY

ANDA: 204403
APPLICANT: Alvogen Pine Brook, Inc.
DRUG PRODUCT: Rivastigmine Transdermal System; 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr

The Division of Bioequivalence II (DBII) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence study and waiver requests will be conducted later. The following deficiency has been identified:

The DBII finds your proposed release specification of (b) (4)% at the 4-hour time point acceptable. However, your proposed release specification of NLT (b) (4)% at the 24-hour time point is not acceptable. Per USP Chapter <1092>, the DBII makes allowances for assay and content uniformity ranges. However, this chapter further states that acceptance criteria including test times are usually established on the basis of an evaluation of the dissolution profile data. Therefore, based on your submitted data, and in accordance with USP Chapter <1092> and Chapter 724, Table 1, the DBII is recommending a release range of (b) (4)% at the 24-hour time point. In the opinion of the DBII, this specification adequately captures the terminal release profile of the test product and ensures better quality control against any possible overage in the future test product batches. Your rationale for a dissolution specification of NLT (b) (4)% at the 24-hour time point is inadequate. Please provide adequate justification for your proposed release specification of NLT (b) (4)% at the 24-hour time point. Alternatively, you may acknowledge the following DB II-recommended dissolution method and revised DB II-recommended release specifications:

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications:

1 hour: (b) (4)
2 hours: (b) (4)
4 hours: (b) (4)
9 hours: (b) (4)
24 hours: (b) (4)

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

ETHAN M STIER
10/08/2013

OSI Consult Request for Biopharmaceutical Inspections	
Date	September 20, 2013
Subject	Request for Biopharmaceutical Inspections (BE)
Addressed to	William H. Taylor, Ph.D. Director, Division of BE and GLP Compliance Office of Scientific Investigations william.taylor1@fda.hhs.gov
Consulting Office/Division	OGD/Division of Clinical Review
Project Manager	Nitin K. Patel, Pharm.D.
Application Type	PEPFAR? ☐ Yes ☒ No ☐ NDA ☐ BLA ☒ ANDA
Application Number	204403
Drug Product	Rivastigmine Transdermal System Extended-release Film, 4.6 mg/24 hr and 9.5 mg/24 hr
Sponsor Name	Alvogen Pine Brook, Inc.
Sponsor Address	10 Bloomfield Avenue, Building B Pine Brook, NJ 07058
US Agent (if applicable)	
US Agent Address	
Electronic Submission	☒ Yes ☐ No
GDUFA Due Date	April 22, 2014
Action Goal Date	January 22, 2014
OSI Review Requested By	John R. Peters, M.D., Director, Division of Clinical Review

Inspection Request Detail (All fields should be fill out completely)			
Study #1			
Study Number	C10-1870 (R10-1318, S11-0069)		
Study Title	A Multiple Site Study to Evaluate the Irritation and Sensitization Potential of Repeat Applications of Rivastigmine 4.6 mg/24 hours Patch (Transdermal System) versus Exelon 4.6 mg/24 hours Patch (Rivastigmine Transdermal System) in Normal Healthy Volunteers		
Study Type	☐ In vivo BE	☐ In vitro BE	☐ Permeability ☒ In vivo Clinical Study
☒ Inspection Request - Clinical Site		☐ Inspection Request - Analytical Site	
Facility #1 Name: Cetero Research – St. Charles Address: 400 Fountain Lakes Blvd. St. Charles, MO 63301 (Tel) 637-947-1200 (Fax)		Facility #1 Name: Address: (Tel) (Fax)	

Clinical Investigator: James C. Freeman, M.D. (email) james.freeman@cetero.com	Principal Analytical Investigator: (email)
Check one: ☐ Routine inspection ☒ For cause	Check one: ☐ Routine inspection ☐ For cause
<i>(please include specific review concerns or items to be addressed during the inspection in the appendix below)</i>	
☒ Study Report: 5.3.1.2.4	☐ Validation Report: (eg., 5.3.1.2) ☐ Bioanalytical Report: (eg., 5.3.1.4)

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, OSI.

I. Appendix

Specific Items To be Addressed During the Inspection
On May 21, 2013, OSI provided their evaluation of the FDA audit of the clinical portions of two studies for (b) (4), conducted at PRACS Institute (Cetero Research, Principal Investigator: James C. Freeman), St. Charles, MO, during (b) (4) by ORA investigators Kathleen B. Swat and Karen M. Montgomery (Kansas District Office). OSI classified this clinical site as OAI and provided the following conclusions: (b) (4) Because of these findings, the OGD Division of Clinical Review is requesting a For-Cause inspection for Dr. James C. Freeman (Site #02), at this time, for ANDA 204403. Attached below is a report of the previous OSI findings.

CLINICAL BIOEQUIVALENCE DEFICIENCY (EASILY CORRECTABLE)

ANDA 204403

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



APPLICANT: Alvogen Pine Brook, Inc.

TEL: [REDACTED] (b) (6)

ATTN: Jasmine Shah
Vice President, Regulatory and Medical Affairs

FAX: (973) 201-1086

FROM: Nitin K. Patel

PROJECT MANAGER: (240) 402-3878
(301) 827-4141 (fax)

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 12, 2012, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Rivastigmine Transdermal System; 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr.

The deficiencies presented below represent EASILY CORRECTABLE DEFICIENCIES identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies with an "EASILY CORRECTABLE DEFICIENCY AMENDMENT" within ten (10) business days. If you do not submit a complete response within ten (10) business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments. In addition, please notify the Project Manager identified above.

A partial response to this fax will not be processed as an amendment and will not start a review. Please submit official archival copies of your response to the ANDA. Please notify the above Project Manager when your amendment has been submitted.

Please direct any questions concerning this communication to the Project Manager identified above.

SPECIAL INSTRUCTIONS:

Your cover letter should clearly indicate that the response is a "*Clinical Bioequivalence Amendment/Easily Correctable Deficiency*". We also request that you include a copy of this communication with your response.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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CLINICAL BIOEQUIVALENCE DEFICIENCY (EASILY CORRECTABLE) TO BE PROVIDED TO THE APPLICANT

ANDA: 204403
APPLICANT: Alvogen Pine Brook, Inc.
DRUG PRODUCT: Rivastigmine Transdermal System; 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr.

In order to assist in the review of the clinical study C10-1870 for ANDA 204403 [A Multiple Site Study to Evaluate the Irritation and Sensitization Potential of Repeat Applications of Rivastigmine 4.6 mg/24 hours Patch (Transdermal System) versus Exelon 4.6 mg/24 hours Patch (Rivastigmine Transdermal System) in Normal Healthy Volunteers], please provide the following information:

Irritation Study:

Request:

Please provide an SAS transport (.xpt) data set that accurately corresponds to the data listing in Appendix 16.1.9, Table 1.1a in the clinical study report.

Comments:

In the data set analysis.xpt included with the application, the last observation carried forward (LOCF) was not provided for irritation score: When the patch was moved, as per the Guidance, due to high irritation scores, in some cases the data from the original site and/or the new site do not appear to be entered nor is the last score from the original site carried forward. Instead those values were recorded as missing. In all cases when the patch was moved, it is not clear whether the score in the .xpt file was from the original site or new site.

For example, according to Table 1.1a, for subject ^{(b) (6)}, the irritation score was 4 on day 7; and the patch was moved to a new site; then moved again on day 13. In file analysis.xpt, the values on day 7 and day 13 are missing. The SAS file did not include all the scores for original site and all the subsequent sites. (Note that this is not an exhaustive list of errors.)

Sensitization Study:

Per your report, there were 229 subjects for test product and 228 subjects for reference product. In both file summary.xpt and analysis.xpt, there were 228 subjects for both.

Please correct the data set or clarify why there is this discrepancy between the study report and the .xpt files.

Sincerely yours,

{See appended electronic signature page}

John R. Peters, M.D.
Director, Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

NITIN K PATEL
07/16/2013

JOHN R PETERS
07/16/2013

CLINICAL BIOEQUIVALENCE DEFICIENCY (EASILY CORRECTABLE)

ANDA 204403

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



APPLICANT: Alvogen Pine Brook, Inc.

TEL: [REDACTED] (b) (4)

ATTN: Jasmine Shah
Vice President, Regulatory and Medical Affairs

FAX: (973) 201-1086

FROM: Nitin K. Patel

PROJECT MANAGER: (240) 276-8670
(240) 276-8966 (fax)

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 12, 2012, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Rivastigmine Transdermal System; 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr.

The deficiencies presented below represent EASILY CORRECTABLE DEFICIENCIES identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies with an "EASILY CORRECTABLE DEFICIENCY AMENDMENT" within ten (10) business days. If you do not submit a complete response within ten (10) business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments. In addition, please notify the Project Manager identified above.

A partial response to this fax will not be processed as an amendment and will not start a review. Please submit official archival copies of your response to the ANDA. Please notify the above Project Manager when your amendment has been submitted.

Please direct any questions concerning this communication to the Project Manager identified above.

SPECIAL INSTRUCTIONS:

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CLINICAL BIOEQUIVALENCE DEFICIENCY (EASILY CORRECTABLE) TO BE PROVIDED TO THE APPLICANT

ANDA: 204403
APPLICANT: Alvogen Pine Brook, Inc.
DRUG PRODUCT: Rivastigmine Transdermal System; 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr.

In order to assist in the review of the clinical study C10-1870 for ANDA 204403 [A Multiple Site Study to Evaluate the Irritation and Sensitization Potential of Repeat Applications of Rivastigmine 4.6 mg/24 hours Patch (Transdermal System) versus Exelon 4.6 mg/24 hours Patch (Rivastigmine Transdermal System) in Normal Healthy Volunteers], please provide the following information:

1. Certification on financial interests and arrangements for Dr. Alan K. Copa.

Sincerely yours,

{See appended electronic signature page}

John R. Peters, M.D.
Director, Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

NITIN K PATEL
06/12/2013

JOHN R PETERS
06/12/2013

BIOEQUIVALENCE AMENDMENT

ANDA 204403

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810



APPLICANT: Alvogen Pine Brook, Inc.

TEL: (b) (6)

ATTN: Jasmine Shah

FAX: (973) 201-1086

FROM: Chitra Mahadevan

FDA CONTACT PHONE: (240) 276-8817

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on June 12, 2012, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Rivastigmine Transdermal System; 4.6 mg/24hr, 9.5 mg/24hr, and 13.3 mg/24 hr.

Reference is also made to your amendments dated April 11, 2013 and May 2, 2013.

The Division of Bioequivalence II has completed its review of the submissions referenced above and has identified deficiencies which are presented on the attached ____ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Dissolution Acknowledgement

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response**.

Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence II, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:

*Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810*

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

Please submit your response in electronic format. This will improve document availability to review staff.

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BIOEQUIVALENCE DEFICIENCY

ANDA: 204403
APPLICANT: Alvogen Pine Brook, Inc.
DRUG PRODUCT: Rivastigmine Transdermal System; 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr

The Division of Bioequivalence II (DBII) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence study will be conducted later. The following deficiency has been identified:

You have conducted acceptable dissolution testing; however, your proposed dissolution specifications are not acceptable. Based on the submitted data, the DBII recommends the following dissolution method and specifications:

Medium: 0.9% NaCl
Volume: 500 mL
Apparatus: Modified USP Type VI (Cylinder)
Speed: 50 rpm
Temperature: 32 °C

Specifications for all strengths (4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr):

1 hr: ^{(b) (4)}
2 hr:
4 hr:
9 hr:
24 hr:

Please acknowledge the above dissolution method and specifications.

Sincerely yours,

{ See appended electronic signature page }

Ethan M. Stier, Ph.D., R.Ph.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

ETHAN M STIER
05/23/2013

ANDA FILING CHECKLIST
(CTD or eCTD FORMAT)
FOR COMPLETENESS AND ACCEPTABILITY of an APPLICATION

ANDA: 204403
 APPLICANT: ALVOGEN PINE BROOK, INC.
 RELATED APPLICATION(S): N/A

DRUG NAME: **RIVASTIGMINE**
 DOSAGE FORM: TRANSDERMAL SYSTEM (PATCH), 4.6 mg/24 hr and 9.5 mg/24 hr and 13.3 mg/24 hr
(NEW STRENGTH 13.3 mg/24 hr)

LETTER DATE: 1/22/2013
 RECEIVED DATE: 1/22/2013

- P-IV
- FIRST GENERIC
- EXPEDITED REVIEW REQUEST: MaPP 5240.1 or MaPP 5240.3 (Approved/Denied)
- PEPFAR
- PET

Electronic or Paper Submission: Gateway

Type II DMF# (b) (4)

BASIS OF SUBMISSION:

NDA/ANDA: NDA 022083
FIRM: NOVARTIS PHARMACEUTICALS CORP.
RLD: EXELON

****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s).**

Review Team:

CHEM Team: DC2 Team 24 ☒ Activity	Bio Team: DBE Team 7, Xiaojian Jiang ☒ Activity
RPM: Linda Park ☒ FYI	Bio PM: Chitra Mahadevan ☒ FYI
CHEM PQRPM: Frank J. Nice ☒ FYI	Clinical Endpoint Team: Carol Kim/Nitin Patel ☒ Activity
CHEM Team Leader: Bing Wu No Assignment Needed in DARRTS	DMF Review Team Leader: ☒ FYI Dave Skanchy
Labeling Reviewer: James Barlow ☒ Activity	Micro Review: ☐ Activity

SPECIAL INSTRUCTIONS FOR DOCUMENT ROOM (applicable only for a response to a refuse to receive):

Regulatory Reviewer: Shannon Hill Date: April 22, 2013	Recommendation: ☒ FILE ☐ REFUSE to RECEIVE

Comments: EC-1
 Therapeutic Code: 2013060 (Drugs for Memory (Alzheimers/Senility/Dementia))
 On Cards: Yes
 Archival copy: Gateway

- For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>
- For a Comprehensive Table of Contents Headings and Hierarchy please go to: <http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf>
- For more CTD and eCTD informational links see the final page of the ANDA Checklist

1. Edit Application Property Type in DARRTS where applicable for

- a. First Generic Received
 Yes No
- b. Market Availability
 Rx OTC
- c. Pepfar
 Yes No
- d. Product Type
 Small Molecule Drug
- e. USP Drug Product (at time of filing review)
 Yes No

2. Edit Submission Patent Records

Yes

3. Edit Contacts Database with Bioequivalence Recordation where applicable

Yes

4. EER (internal notation: RSB to submit at time of filing)

Yes

5. GDUFA Obligation Met (internal notation-if not met contact: cder-om-collection@fda.hhs.gov)

Yes

ADDITIONAL COMMENTS REGARDING THE ANDA:

NEW STRENGTH AMENDMENT:

1. Ask applicant to submit an updated Debarment Certification; *received 4/22/2013*
2. Ask applicant to submit an updated cGMP from Alvogen (applicant); *received 4/22/2013*
3. Ask applicant to provide the master manufacturing batch records that indicate the maximum batch size; *received 4/22/2013*
4. Ask applicant to submit 6 months of stability data per commitment in the cover letter; also submit data for 3 batches of this new strength (only one batch submitted) ; *received 4/22/2013 (6 months stability data for batch C0014AL0BC and 3 months data for the 2 additional batches with only 3 time points); refer to the email attachment below for the commitment to submit 6 months data for the two additional batches*
5. Left a voice message for Dr. Shah on 4/17/2013

Dear Dr. Hill

We submit the 6 month stability for the exhibit batch but only 3 months of stability is available for the 2 additional batches. Also, we are committing to submit the 6 month stability data for the two additional batches when they become available.

Please advise when I could call you or you could call me at (b) (6)

Regards

Jasmine

Reference ID: 3308350

From: Hill, Shannon [mailto:Shannon.Hill@fda.hhs.gov]

Sent: Tuesday, April 23, 2013 10:41 AM

To: Shah, Jasmine

Subject: RE: ANDA 204403

Hi Dr. Shah,

I tried calling you just now. It appears that the stability data for the 2 additional batches are incomplete. We want to see at least 6 months of accelerated stability data for completeness. Also, the ANDA indicates that the proposed commercial batch size is (b) (4) patches. Your amendment directs me to the original master batch records which indicate a maximum batch size of (b) (4). Can you provide a statement or direct me to the location in the ANDA that indicates that (b) (4) patches is equivalent to the kg weight provided?

We will have to hold off the acknowledgement of the additional strength until the stability data is complete. Please provide it as soon as completed.

Thanks,
Shannon

From: Shah, Jasmine [mailto:Jasmine.Shah@alvogen.com]

Sent: Monday, April 22, 2013 4:37 PM

To: Hill, Shannon

Subject: RE: ANDA 204403

Dear Shannon

Thanks you for getting back to us. As requested, we have submitted the information through gateway. Attached is a copy of the cover letter for your reference. We tried to call you couple of times as we wanted to inform you that the response will be sent today as the stability pull date was Friday, April 19 and we wanted to send you the data. Please advise if you need any further information. Also, Melissa Henry is no longer with Alvogen at this time. She has decided to pursue other opportunities.

Regards

Jasmine Shah, MS, R.Ph.

VP Regulatory and Medical Affairs

Jasmine.shah@alvogen.com

10 Bloomfield Avenue, Building B

Pine Brook, NJ 07058

Tel. 973 852 7832

(b) (4)

alvogen.com

The information contained herein is intended only for the addressee identified above. It may be or include material which is confidential. If you are not the intended recipient, or a person responsible for delivering this message to the intended recipient, you are hereby notified that the unauthorized use, disclosure, distribution or copying is prohibited. If you have received this transmission in error, please immediately notify the sender.

From: Hill, Shannon [mailto:Shannon.Hill@fda.hhs.gov]

Sent: Wednesday, April 17, 2013 4:19 PM

To: Shah, Jasmine

Cc: Henry, Melissa

Subject: ANDA 204403

Hi Dr. Shah,

I left you a voicemail message regarding the new strength amendment for ANDA 204403. Please address/submit the following to complete the ANDA:

1. Ask applicant to submit an updated debarment certification
2. Ask applicant to submit an updated cGMP from Alvogen (applicant)
3. Ask applicant to provide the master manufacturing batch records that indicate the maximum batch size (the current one does not indicate the batch size)
4. Ask applicant to submit 6 months of stability data per commitment in the cover letter; also submit data for 3 batches of this new strength (only one batch submitted)

Thanks,
Shannon
Reference ID: 3308350

MODULE 1: ADMINISTRATIVE

		COMMENT (S)																																				
1.1	1.1.2 Signed and Completed Application Form (356h) (Rx/OTC Status) (original signature) Refer to the links provided for the newly revised form 356h and updated instructions. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM321897.pdf http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/ucm082348.pdf ** PLACE ESTABLISHMENT CONTACT INFORMATION IN SECTION 29: MANUFACTURING STEPS AND/OR TYPE OF TESTING (INCLUDE US AGENT INFORMATION IF APPLICABLE)**																																					
1.2	Cover Letter Yes																																					
1.2.1	Form FDA 3674 (PDF) B	REFER TO ORIGINAL ANDA																																				
*	Table of Contents (paper submission only) N/A																																					
1.3.2	Field Copy Certification (N/A for E-Submissions) N/A (original signature)																																					
1.3.3	Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other: (no qualifying statement) 1. Debarment Certification (original signature) Yes 2. List of Convictions statement (original signature) Yes																																					
1.3.4	Financial Certifications Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) N/A Disclosure Statement (Form FDA 3455) N/A	REFER TO ORIGINAL ANDA																																				
1.3.5	Patent Information Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations Patent Certification 1. Patent number(s) PIII: 5602176 PIV: 6316023 & 6335031 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ (Statement of Notification) ☒ 3. Expiration of Patent(s): 1/8/2019 a. Pediatric exclusivity submitted? N/A b. Expiration of Pediatric Exclusivity? N/A 4. Exclusivity Statement: State marketing intentions? Yes, will not market prior to expiration of the New Strength exclusivity Patent and Exclusivity Search Results from query on Appl No 022083 Product 005 in the OB_Rx list. <table border="1"> <thead> <tr> <th>Appl No</th> <th>Prod No</th> <th>Patent No</th> <th>Patent Expiration</th> <th>Drug Substance Claim</th> <th>Drug Product Claim</th> <th>Patent Use Code</th> </tr> </thead> <tbody> <tr> <td>N022083</td> <td>005</td> <td>5602176</td> <td>Feb 11, 2014</td> <td>Y</td> <td>Y</td> <td>U - 322</td> </tr> <tr> <td>N022083</td> <td>005</td> <td>6316023</td> <td>Jan 8, 2019</td> <td></td> <td>Y</td> <td></td> </tr> <tr> <td>N022083</td> <td>005</td> <td>6335031</td> <td>Jan 8, 2019</td> <td></td> <td>Y</td> <td></td> </tr> </tbody> </table> U - 322 TREATMENT OF ALZHEIMER'S DEMENTIA Exclusivity Data <table border="1"> <thead> <tr> <th>Appl No</th> <th>Prod No</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td>N022083</td> <td>005</td> <td>NS</td> <td>Aug 31, 2015</td> </tr> </tbody> </table> NS NEW STRENGTH	Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	N022083	005	5602176	Feb 11, 2014	Y	Y	U - 322	N022083	005	6316023	Jan 8, 2019		Y		N022083	005	6335031	Jan 8, 2019		Y		Appl No	Prod No	Exclusivity Code	Exclusivity Expiration	N022083	005	NS	Aug 31, 2015	
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N022083	005	NS	Aug 31, 2015																																			

1.4.1	References Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient Yes b. Type II DMF# (b) (4) c. Type III DMF authorization letter(s) for container closure Yes; (b) (4) 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) Yes MF (b) (4) RIVASTIGMINE AS MANUFACTURED IN BARCELONA SPAIN <table border="1"> <tr> <td>Application Status</td> <td>Active</td> </tr> <tr> <td>Status Date</td> <td>08/03/2009</td> </tr> <tr> <td>Status Change Reason</td> <td></td> </tr> <tr> <td>Holder Name & Address</td> <td>(b) (4)</td> </tr> <tr> <td>MF Type</td> <td>Type II</td> </tr> <tr> <td>Responsible Organization</td> <td>CDER/OBI/DRM</td> </tr> <tr> <td>User Fees Obligation</td> <td>Met</td> </tr> </table>	Application Status	Active	Status Date	08/03/2009	Status Change Reason		Holder Name & Address	(b) (4)	MF Type	Type II	Responsible Organization	CDER/OBI/DRM	User Fees Obligation	Met	
Application Status	Active															
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Status Change Reason																
Holder Name & Address	(b) (4)															
MF Type	Type II															
Responsible Organization	CDER/OBI/DRM															
User Fees Obligation	Met															
1.12.4	Request for Comments and Advice - Proprietary name requested No If Yes, did the firm provide the request as a separate electronic amendment labeled "Proprietary Name Request" at initial time of filing 1. Yes N/A 2. No - contact the firm to submit the request as a separate electronic amendment.															
1.12.11	Basis for Submission NDA#: NDA 022083 Ref Listed Drug: EXELON Firm: NOVARTIS PHARMACEUTICALS CORP ANDA suitability petition required? N/A If Yes, provide petition number and copy of approved petition ANDA Citizen's Petition Required? N/A If Yes, provide petition number and copy of petition															
1.12.12	Comparison between Generic Drug and RLD-505(j)(2)(A) 1. Conditions of use Same as RLD 2. Active ingredients Select 3. Inactive ingredients Justified 4. Route of administration Same as RLD 5. Dosage Form Same as RLD 6. Strength Same as RLD															
1.12.14	Environmental Impact Analysis Statement (cite 21CFR 25.31, if applicable) Yes															
1.12.15	Request for Waiver Request for Waiver of In-Vivo BA/BE Study(ies) Yes															
1.14.1	Draft Labeling (Multi Copies N/A for E-Submissions) 1.14.1.1 4 copies of draft for paper submission only (each strength and container) Yes 1.14.1.2 1 side by side labeling comparison of containers and carton with all differences visually highlighted and annotated Yes 1.14.1.3 1 package insert (content of labeling) and SPL submitted electronically Yes															

	HOW SUPPLIED: Rivastigmine Patch 4.6 mg/24 hours Each patch of 4.6 cm² contains 6.9 mg rivastigmine with <i>in-vivo</i> release rate of 4.6 mg/24 hours. Carton of 30.....NDC (b) (4) Rivastigmine Patch 9.5 mg/24 hours Each patch of 9.2 cm² contains 13.8 mg rivastigmine with <i>in-vivo</i> release rate of 9.5 mg/24 hours. Carton of 30.....NDC (b) (4) Rivastigmine Patch 13.3 mg/24 hours Each patch of 13.8 cm² contains 20.7 mg rivastigmine with <i>in-vivo</i> release rate of 13.3 mg/24 hours. Carton of 30.....NDC (b) (4)	
1.14.3	Listed Drug Labeling 1.14.3.1 1 side by side labeling (package and patient insert) comparison with all differences visually highlighted and annotated Yes 1.14.3.3 RLD package insert, 1 RLD label and 1 RLD container label Yes	

MODULE 2: Quality Overall Summary

	REFER TO ORIGINAL ANDA	COMMENT (S)
2.3	Quality Overall Summary (QOS) E-Submission: PDF N/A Word Processed e.g., MS Word N/A A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ Question based Review (QbR) N/A 2.3.S Drug Substance (Active Pharmaceutical Ingredient) N/A 2.3.S.1 General Information 2.3.S.2 Manufacture 2.3.S.3 Characterization 2.3.S.4 Control of Drug Substance 2.3.S.5 Reference Standards or Materials 2.3.S.6 Container Closure System 2.3.S.7 Stability 2.3.P Drug Product N/A 2.3.P.1 Description and Composition of the Drug Product 2.3.P.2 Pharmaceutical Development 2.3.P.2.1 Components of the Drug Product 2.3.P.2.1.1 Drug Substance 2.3.P.2.1.2 Excipients 2.3.P.2.2 Drug Product Oral Solids: Immediate Release or Modified Release (Matrix Technology or Compressed Film Coated Components) tablet scoring data per Draft <i>Guidance for Industry, Tablet Scoring: Nomenclature, Labeling and Data for Evaluation</i> (if applicable) 2.3.P.2.3 Manufacturing Process Development 2.3.P.2.4 Container Closure System 2.3.P.3 Manufacture 2.3.P.4 Control of Excipients 2.3.P.5 Control of Drug Product 2.3.P.6 Reference Standards or Materials 2.3.P.7 Container Closure System 2.3.P.8 Stability	

MODULE 3: 3.2.S DRUG SUBSTANCE

		COMMENT (S)																																
3.2.S.1	General Information) N/A (Do not refer to DMF) 3.2.S.1.1 Nomenclature 3.2.S.1.2 Structure 3.2.S.1.3 General Properties	REFER TO ORIGINAL ANDA																																
3.2.S.2	Manufacturer Drug Substance (Active Pharmaceutical Ingredient) Must correlate to the establishment information submitted in annex to Form FDA 356h. 1. Name and Full Address(es)of the Facility(ies) Yes 2. Contact name, phone and fax numbers, email address Yes 3. U.S Agent’s name (if applicable) Yes 4. Specify Function or Responsibility Yes 5. Type II DMF number for API Yes 6. CFN, FEI or DUNS numbers (if available) Yes <table border="1" data-bbox="250 667 1286 1142"> <tr> <td>Manufacturing and Testing Site</td> <td>(b) (4)</td> </tr> <tr> <td>Address:</td> <td></td> </tr> <tr> <td>Responsibility</td> <td>Manufacturing, testing, packing, labeling, release and storage of Rivastigmine</td> </tr> <tr> <td>Contact Person:</td> <td>(b) (4)</td> </tr> <tr> <td>Phone No.</td> <td></td> </tr> <tr> <td>Fax No.</td> <td></td> </tr> <tr> <td>E-mail</td> <td></td> </tr> <tr> <td>FEI Number</td> <td></td> </tr> <tr> <td>DUNS</td> <td></td> </tr> </table> <table border="1" data-bbox="250 1167 1286 1549"> <tr> <td>US Agent</td> <td>(b) (4)</td> </tr> <tr> <td>Address:</td> <td></td> </tr> <tr> <td>Responsibility</td> <td></td> </tr> <tr> <td>Contact Person:</td> <td></td> </tr> <tr> <td>Phone No.</td> <td></td> </tr> <tr> <td>Fax No.</td> <td></td> </tr> <tr> <td>E-mail</td> <td></td> </tr> </table> The drug substance, Rivastigmine, manufactured by (b) (4) is consistent with the procedures and controls described in Drug Master File (DMF) No. (b) (4) on file with FDA.	Manufacturing and Testing Site	(b) (4)	Address:		Responsibility	Manufacturing, testing, packing, labeling, release and storage of Rivastigmine	Contact Person:	(b) (4)	Phone No.		Fax No.		E-mail		FEI Number		DUNS		US Agent	(b) (4)	Address:		Responsibility		Contact Person:		Phone No.		Fax No.		E-mail		
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Address:																																		
Responsibility																																		
Contact Person:																																		
Phone No.																																		
Fax No.																																		
E-mail																																		
3.2.S.3	Characterization N/A Provide the following in tabular format: 1. Name of Impurity(ies) 2. Structure of Impurity(ies) 3. Origin of Impurity(ies)	REFER TO ORIGINAL ANDA																																

3.2.S.4	Control of Drug Substance (Active Pharmaceutical Ingredient) 3.2.S.4.1 Specification Testing specifications and data from drug substance manufacturer(s) N/A NO UPDATES SUBMITTED 3.2.S.4.2 Analytical Procedures N/A NO UPDATES SUBMITTED 3.2.S.4.3 Validation of Analytical Procedures (API that is USP or reference made to DMF, must provide verification of USP or DMF procedures) N/A 1. Spectra and chromatograms for reference standards and test samples N/A NO UPDATES SUBMITTED 2. Samples-Statement of Availability and Identification of: a. Drug Substance Yes b. API lot number(s) 3.2.S.4.3 Samples – Statement of Availability and Identification (Rivastigmine) As per 21 CFR 314.50(c), samples of the following are available on-site at (b) (4) (b) (4). Samples will be supplied upon request by the Agency. The drug substance (Rivastigmine) utilized in the manufacture of the exhibit lot of Rivastigmine Transdermal System, 13.3 mg/24 hr and the reference standards utilized to test the drug substance are identified in the tables below. Drug Substance <table border="1" data-bbox="250 722 943 823"> <thead> <tr> <th data-bbox="250 722 581 772">Manufacturer Batch #</th> <th data-bbox="581 722 943 772">(b) (4)</th> </tr> </thead> <tbody> <tr> <td data-bbox="250 772 581 823">A11225A</td> <td data-bbox="581 772 943 823">001112</td> </tr> </tbody> </table> 3.2.S.4.4 Batch Analysis 1. COA(s) specifications and test results from drug substance mfgr(s) Yes 2. Drug Product manufacturer’s certificate of analysis Yes 3.2.S.4.5 Justification of Specification N/A NO UPDATES SUBMITTED	Manufacturer Batch #	(b) (4)	A11225A	001112	
Manufacturer Batch #	(b) (4)					
A11225A	001112					
3.2.S.5	Reference Standards or Materials (Do not refer to DMF) Yes					
3.2.S.6	Container Closure Systems N/A NO UPDATES SUBMITTED					
3.2.S.7	Stability 1. Retest date or expiration date of API N/A NO UPDATES SUBMITTED					

MODULE 3: 3.2.P DRUG PRODUCT

		COMMENT (S)
3.2.P.1	Description and Composition of the Drug Product 1. Unit composition with indication of the function of the inactive ingredient(s) Yes 2. Inactive ingredients and amounts are appropriate per IIG (per/dose justification) Yes; 3. Conversion from % to mg/dose values for inactive ingredients (if applicable) N/A 4. Elemental iron: provide daily elemental iron calculation or statement of adherence to 21CFR73.1200 (calculation of elemental iron intake based on maximum daily dose (MDD) of the drug product is preferred if this section is applicable) N/A 5. Injections: If the reference listed drug is packaged with a drug specific diluent then the diluent must be Q1/Q2 and must be provided in the package configuration N/A	
3.2.P.2	Pharmaceutical Development 1. Pharmaceutical Development Report Yes	
3.2.P.3	Manufacture 3.2.P.3.1 Drug Product Must correlate to the establishment information submitted in annex to Form FDA 356h for the finished dosage manufacturer and all outside contract testing laboratories. 1. Name and Full Address(es) of the Facility(ies) Yes 2. Contact name, phone and fax numbers, email address Yes 3. U.S Agent’s name (if applicable) N/A 4. Specify Function or Responsibility Yes	

5. CGMP Certification (from both applicant and drug product manufacturer if different entities) Yes

6. CFN, FEI or DUNS numbers (if available) Yes

Rivastigmine Transdermal System, 13.3 mg/24 hr, will be manufactured, tested, packaged and labeled at the same facility listed in the Original ANDA (Sequence 0000), Submitted on June 11, 2012. The information for the finished product manufacturer is provided below for ease of review.

Manufacturing and Testing Site	(b) (4)
Address	(b) (4)
Responsibility	• Drug substance and finished product analytical testing and release. • Inactive ingredients and packaging components analytical testing and release. • Finished product pharmaceutical manufacturing, packaging and labeling. • Intermediate, finished product and stability testing. • Finished product storage.
Contact Person	(b) (4)
Establishment Registration No.	(b) (4)
DUNS No.	(b) (4)
Fax No.	(b) (4)

3.2.P.3.2 Batch Formula Yes

3.2.P.3.3 Description of Manufacturing Process and Process Controls

1. Description of the Manufacturing Process Yes
2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified Yes
3. Master packaging records for intended marketing container(s) Yes
4. If sterile product N/A
5. Reprocessing Statement (cite 21CFR 211.115, submitted by the drug product manufacturer and the applicant, if different entities) Yes

3.2.P.3.4 Controls of Critical Steps and Intermediates Yes

3.2.P.3.5 Process Validation and/or Evaluation

1. Microbiological sterilization validation N/A
2. Filter validation (if aseptic fill) N/A

PROPOSED COMMERCIAL BATCH SIZE: (copied from batch formula in 3.2.P.3.2)

ANDA BATCH: (b) (4) patches

COMMERCIAL: (b) (4) patches

3.2.P.4 Controls of Excipients (Inactive Ingredients)

Source of inactive ingredients identified Yes

3.2.P.4.1 Specifications

1. Testing specifications (including identification and characterization) No; **NO**

UPDATES SUBMITTED

2. Suppliers' COA (specifications and test results) Yes

3.2.P.4.2 Analytical Procedures N/A

3.2.P.4.3 Validation of Analytical Procedures N/A

3.2.P.4.4 Justification of Specifications:

1. Applicant COA Yes

MODULE 3: 3.2.P DRUG PRODUCT (Continued)

		COMMENT (S)																	
3.2.P.5	Controls of Drug Product 3.2.P.5.1 Specification(s) Yes 3.2.P.5.2 Analytical Procedures Yes 3.2.P.5.3 Validation of Analytical Procedures (if using USP procedure, must provide verification of USP procedure) N/A Samples - Statement of Availability and Identification of: 1. Finished Dosage Form Yes 2. Lot number(s) and strength of Drug Product(s) 3.2.P.5.3 Samples – Statement of Availability and Identification As per 21 CFR 314.50(e), samples of the following are available on-site at (b) (4) (b) (4) Samples will be supplied upon request by the Agency. Materials utilized in the manufacture, testing, and packaging of exhibit Lot C0014AL0BC of Rivastigmine Transdermal System 13.3 mg/24 hr are identified in the tables below. Drug Substance: Rivastigmine <table border="1" data-bbox="293 867 1105 961"> <thead> <tr> <th data-bbox="293 867 631 913">Manufacturer Batch #</th> <th data-bbox="631 867 1105 913">(b) (4)</th> </tr> </thead> <tbody> <tr> <td data-bbox="293 913 631 961">A11225A</td> <td data-bbox="631 913 1105 961">001112</td> </tr> </tbody> </table> Reference Standards <table border="1" data-bbox="293 1041 1289 1180"> <thead> <tr> <th data-bbox="293 1041 688 1087">Standards</th> <th data-bbox="688 1041 911 1087">Source</th> <th data-bbox="911 1041 1289 1087">Lot #</th> </tr> </thead> <tbody> <tr> <td data-bbox="293 1087 688 1134">Rivastigmine</td> <td data-bbox="688 1087 911 1134">(b) (4)</td> <td data-bbox="911 1087 1289 1134">43500</td> </tr> <tr> <td data-bbox="293 1134 688 1180">Rivastigmine R-Enantiomer</td> <td data-bbox="688 1134 911 1180">(b) (4)</td> <td data-bbox="911 1134 1289 1180">40065</td> </tr> </tbody> </table> Drug Product <table border="1" data-bbox="293 1262 1289 1356"> <thead> <tr> <th data-bbox="293 1262 792 1308">Product</th> <th data-bbox="792 1262 1289 1308">Batch #</th> </tr> </thead> <tbody> <tr> <td data-bbox="293 1308 792 1356">Rivastigmine Transdermal System, 13.3 mg/24 hr</td> <td data-bbox="792 1308 1289 1356">C0014AL0BC</td> </tr> </tbody> </table> 3.2.P.5.4 Batch Analysis Certificate of Analysis for Finished Dosage Form Yes 3.2.P.5.5 Characterization of Impurities N/A; NO UPDATES SUBMITTED 3.2.P.5.6 Justification of Specifications Yes	Manufacturer Batch #	(b) (4)	A11225A	001112	Standards	Source	Lot #	Rivastigmine	(b) (4)	43500	Rivastigmine R-Enantiomer	(b) (4)	40065	Product	Batch #	Rivastigmine Transdermal System, 13.3 mg/24 hr	C0014AL0BC	
Manufacturer Batch #	(b) (4)																		
A11225A	001112																		
Standards	Source	Lot #																	
Rivastigmine	(b) (4)	43500																	
Rivastigmine R-Enantiomer	(b) (4)	40065																	
Product	Batch #																		
Rivastigmine Transdermal System, 13.3 mg/24 hr	C0014AL0BC																		
3.2.P.7	Container Closure System 1. Summary of Container/Closure System (if new resin, provide data) Yes 2. Components Specification and Test Data Yes 3. Packaging Configuration and Sizes Yes 4. Container/Closure Testing (recommended additional testing for all plastic)N/A a. Solid Orals: water permeation, light transmissionN/A b. Liquids: leachables, extractables, light transmissionN/A 5. Source of supply and suppliers address Yes																		

Table 1		
Container Closure System for Rivastigmine Transdermal System, 13.3 mg/24 hr		
Strength	Description of Container/Closure System	
13.3 mg/24 hr	1 Transdermal System packaged into a multi-laminate, child proof, foil pouch.	

3.2.P.8	3.2.P.8.1 Stability (Finished Dosage Form) 1. Stability Protocol submitted Yes 2. Expiration Dating Period 24 months 3.2.P.8.2 Post-approval Stability and Conclusion Post Approval Stability Protocol and Commitments Yes 3.2.P.8.3 Stability Data 1. Accelerated stability data a. four (4) time points 0,1,2,3 Yes -OR- b. three (3) time points 0,3,6 (if 3 time points for accelerated stability data are submitted then provide 3 exhibit batches along with 12 months of room temperature stability data –Refer to Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products November 2003, Section B) N/A c. for liquid products, inverted or horizontal storage orientation N/A 2. Batch numbers on stability records the same as the test batch Yes 3. Date accelerated stability samples placed in stability chamber Yes 4. Date accelerated stability sample removed from stability chamber for each testing time point Yes	

Stability

Batch	Dosage strength	API manufacturer	Manufacturing date	Start of Stability study	Stability data available
C0014AL0BC	13.3 mg/24 hr				(b) (4)
C0016AL0BC	13.3 mg/24 hr				
C0018AL0BC	13.3 mg/24 hr				

MODULE 3: 3.2.R REGIONAL INFORMATION (Drug Substance)

		COMMENT (S)
3.2.R Drug Substance	3.2.R.1.S Executed Batch Records for drug substance (if available) N/A 3.2.R.2.S Comparability Protocols N/A 3.2.R.3.S Methods Validation Package Yes Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs)	

MODULE 3: 3.2.R REGIONAL INFORMATION (Drug Product)

		COMMENT (S)
3.2.R Drug Product	3.2.R.1.P.1 Executed Batch Records Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation Yes A.) Reconciliations and Yields of Intermediates for the Finished Product Batch # C0014AL0BC  (b) (4)	

Following this page, 1 Page Withheld in Full as (b)(4)

(b) (4)

(b) (4)

Bulk Package Reconciliation required if bulk packaging is used to achieve the minimum package requirement. Provide the following information in their respective sections:

- a. Bulk Package Label (1.14.1) N/A
- b. Bulk Package Stability (accelerated stability data [0,1,2,3] **-OR-** room temperature [0,3,6]) (3.2.P.8) N/A
- c. Bulk Package Container and Closure information (3.2.P.7) N/A

3.2.R.1.P.2 Information on Components Yes

3.2.R.2.P Comparability Protocols N/A

3.2.R.3.P Methods Validation Package Yes

Methods Validation Package (3 copies for paper and N/A for E-Submissions)

(Required for Non-USP drugs)

MODULE 5: CLINICAL STUDY REPORTS

		COMMENT (S)
5.2	Tabular Listing of Clinical Studies N/A	
5.3.1 (complete study data)	Bioavailability/Bioequivalence 1. Formulation data same? a. Comparison of all Strengths (proportionality of multiple strengths) N/A b. Parenterals, Ophthalmics, Otics and Topicals (21 CFR 314.94 (a)(9)(iii)-(v) N/A 2. Lot Numbers and strength of Products used in BE Study(ies) N/A 3. Study Type: IN-VIVO PK STUDY(IES) (Continue with the appropriate study type box below)	
	See Module 2.7 Clinical Summary for placement of BA/BE Summary for tables 9 – 16. The study data that support the BA/BE summary tables should be provided in the corresponding sections below: 5.3.1.2 Comparative BA/BE Study Reports 5.3.1.3 In Vitro-In-Vivo Correlation Study Reports (exception: all dissolution data should be placed in 2.7) 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies Case Report Forms should be placed under the study to which they pertain, and appropriately tagged. Refer to The eCTD Backbone File Specification for Study Tagging //www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf	
5.4	Literature References	
	Possible Study Types:	
Study Type	IN-VIVO BE STUDY(IES) with PK ENDPOINTS (i.e., fasting/fed/sprinkle) 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Select 2. EDR Email: Data Files Submitted Select 3. In-Vitro Dissolution Select	
Study Type	IN-VIVO BE STUDY with CLINICAL ENDPOINTS 1. Properly defined BE endpoints (eval. by Clinical Team) Select 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80,1.25) Select 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) Select 4. EDR Email: Data Files Submitted Select	
Study Type	IN-VITRO BE STUDY(IES) (i.e., in vitro binding assays) Select 1. Study(ies) meets BE criteria (90% CI of 80-125) Select 2. EDR Email: Data Files Submitted Select 3. In-Vitro Dissolution Select	
Study Type	NASALLY ADMINISTERED DRUG PRODUCTS 3. In-Vitro Dissolution (Q1/Q2 sameness) Select	

Type	a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) Select 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study Select 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) Select 2. EDR Email: Data Files Submitted Select b. In-Vivo BE Study with Clinical End Points Select 1. Properly defined BE endpoints (eval. by Clinical Team) Select 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) Select 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) Select 4. EDR Email: Data Files Submitted Select c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) Select	
Study Type	IN-VIVO BE STUDY(IES) with PD ENDPOINTS (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) Select 2. Pivotal Study (study meets BE criteria 90%CI of 80-125) Select	
Study Type	TRANSDERMAL DELIVERY SYSTEMS 1. <u>In-Vivo PK Study</u> Select a. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) Select b. In-Vitro Dissolution Select c. EDR Email: Data Files Submitted Select 2. <u>Adhesion Study</u> Select 3. <u>Skin Irritation/Sensitization Study</u> Select	

Updated 11/27/2012

Active Ingredient Search - Windows Internet Explorer

http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

Active Ingredient Search Results from "OB_Rx" table for query on "rivastigmine."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N022083		No	RIVASTIGMINE	FILM, EXTENDED RELEASE; TRANSDERMAL	13.3MG/24HR	EXELON	NOVARTIS
N022083		No	RIVASTIGMINE	FILM, EXTENDED RELEASE; TRANSDERMAL	13.3MG/24HR	EXELON	NOVARTIS
N022083		No	RIVASTIGMINE	FILM, EXTENDED RELEASE; TRANSDERMAL	4.6MG/24HR	EXELON	NOVARTIS
N022083		No	RIVASTIGMINE	FILM, EXTENDED RELEASE; TRANSDERMAL	4.6MG/24HR	EXELON	NOVARTIS
N022083		Yes	RIVASTIGMINE	FILM, EXTENDED RELEASE; TRANSDERMAL	9.5MG/24HR	EXELON	NOVARTIS
N022083		Yes	RIVASTIGMINE	FILM, EXTENDED RELEASE; TRANSDERMAL	9.5MG/24HR	EXELON	NOVARTIS
A091689	AB	No	RIVASTIGMINE TARTRATE	CAPSULE; ORAL	EQ 1.5MG BASE	RIVASTIGMINE TARTRATE	ALEMBIC PHARMS LTD
A091689	AB	No	RIVASTIGMINE TARTRATE	CAPSULE; ORAL	EQ 1.5MG BASE	RIVASTIGMINE TARTRATE	ALEMBIC PHARMS LTD
A091689	AB	No	RIVASTIGMINE TARTRATE	CAPSULE; ORAL	EQ 3MG BASE	RIVASTIGMINE TARTRATE	ALEMBIC PHARMS LTD
A091689	AB	No	RIVASTIGMINE TARTRATE	CAPSULE; ORAL	EQ 3MG BASE	RIVASTIGMINE TARTRATE	ALEMBIC PHARMS LTD
A091689	AB	No	RIVASTIGMINE TARTRATE	CAPSULE; ORAL	EQ 4.5MG BASE	RIVASTIGMINE TARTRATE	ALEMBIC PHARMS LTD
A091689	AB	No	RIVASTIGMINE TARTRATE	CAPSULE; ORAL	EQ 4.5MG BASE	RIVASTIGMINE TARTRATE	ALEMBIC PHARMS LTD
A091689	AB	No	RIVASTIGMINE TARTRATE	CAPSULE; ORAL	EQ 6MG BASE	RIVASTIGMINE TARTRATE	ALEMBIC PHARMS LTD

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Orange Book Detail Record Search - Windows Internet Explorer

http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=022083&TABLE1=OB_Rx

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Page Tools

Active Ingredient: RIVASTIGMINE
Dosage Form;Route: FILM, EXTENDED RELEASE; TRANSDERMAL
Proprietary Name: EXELON
Applicant: NOVARTIS
Strength: 13.3MG/24HR
Application Number: N022083
Product Number: 005
Approval Date: Aug 31, 2012
Reference Listed Drug: No
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: [View](#)

Active Ingredient: RIVASTIGMINE
Dosage Form;Route: FILM, EXTENDED RELEASE; TRANSDERMAL
Proprietary Name: EXELON
Applicant: NOVARTIS
Strength: 13.3MG/24HR
Application Number: N022083
Product Number: 005
Approval Date: Aug 31, 2012
Reference Listed Drug: No
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: [View](#)

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Patent and Exclusivity Search Results - Windows Internet Explorer

http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexchnew.cfm?Appl_No=022083&Product_No=005&table1=OB_Rx

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FDA Home Drug Databases Orange Book

Patent and Exclusivity Search Results from query on Appl No 022083 Product 005 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N022083	005	5602176	Feb 11, 2014	Y	Y	U - 322	
N022083	005	6316023	Jan 8, 2019		Y		
N022083	005	6335031	Jan 8, 2019		Y		

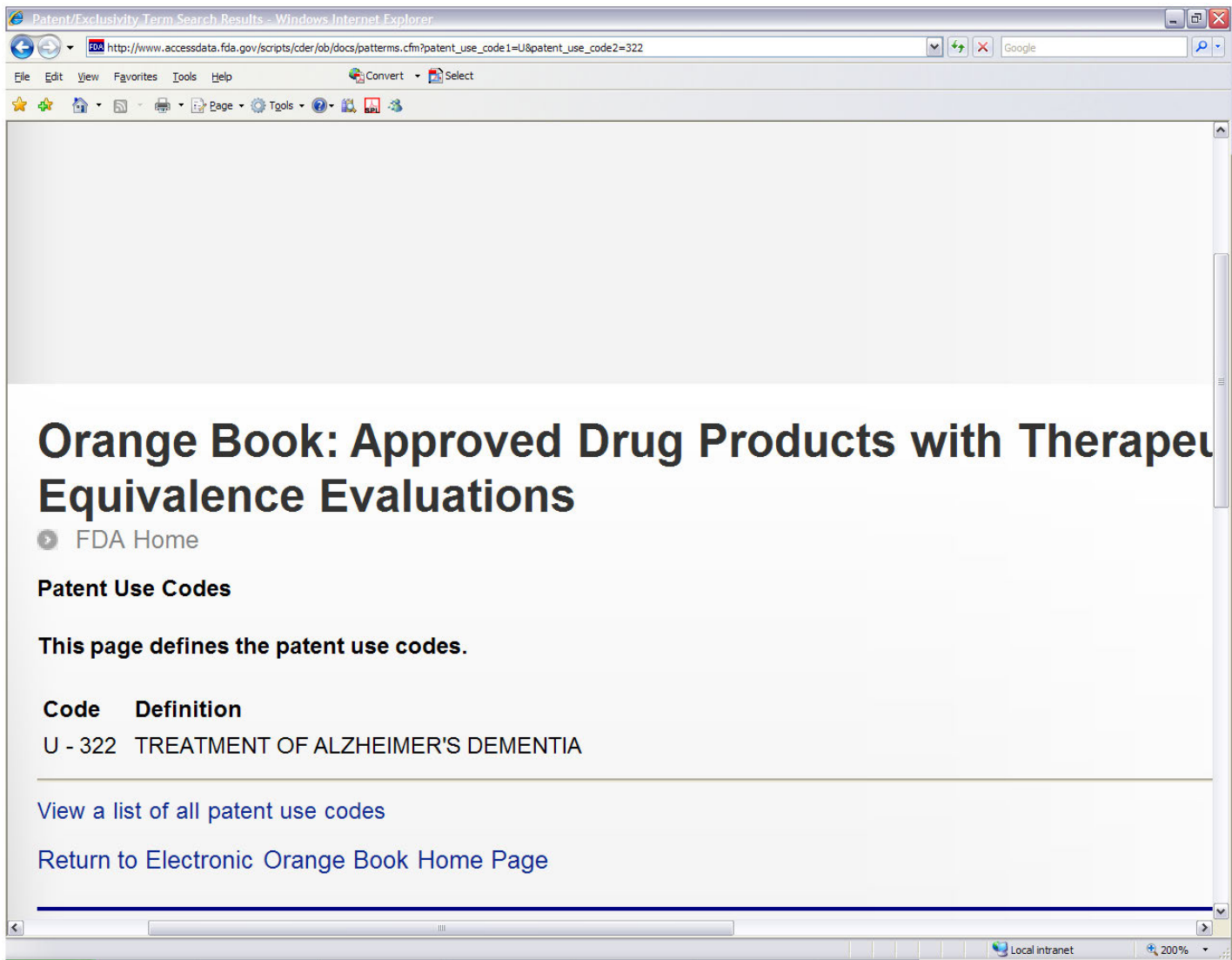
Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
N022083	005	NS	Aug 31, 2015

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be respect to other claims which may apply.

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Patent/Exclusivity Term Search Results - Windows Internet Explorer
http://www.accessdata.fda.gov/scripts/cder/ob/docs/exclterms.cfm?exclusivity_code1=NS&exclusivity_code2=

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

FDA Home

Exclusivity Codes

This page defines the exclusivity codes.

Code Definition
NS NEW STRENGTH

[View a list of all exclusivity codes](#)

[Return to Electronic Orange Book Home Page](#)

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through February 2013

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(b) (4)

Table 6 Formulation Data

Component	Function	Amount in dried matrix / %	Amount mg in 4.6 mg/24 hr Patch Size: 4.6 cm ²	Amount mg in: 9.5 mg/24 hr Patch Size: 9.2 cm ²	Amount mg in: 13.3 mg/24 hr Patch Size: 13.8 cm ²
Active layer, target area weight:	(b) (4)				
Rivastigmine	API	25	6.9 mg	13.8 mg	20.7
(b) (4)					

Inactive Ingredient Database (IID) Comparison:

As per the requirements of 21 CFR 314.94(a)(9)(ii): “Unless otherwise stated in paragraphs (a)(9)(iii) through (a)(9)(v) of this section, an applicant shall identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety of the proposed drug product.”

All inactive ingredients (or their components) utilized in the formulation are listed in the FDA’s Inactive Ingredient Database (IID) and are within or below the listed levels for Transdermal products. The list of the components and the levels utilized in proposed formulation are provided in the table below.

The maximum daily dose for Rivastigmine Transdermal System is 13.3 mg/24 hr. Only one transdermal system of either the 4.6 mg/24 hr, 9.5 mg/24 hr and 13.3 mg/24hr strengths are to be worn at any given time, according to the package insert for the RLD (Exelon® Patch). Additionally, the patient leaflet for the RLD (Exelon® Patch) states that every 24 hours the transdermal system should be removed and a new transdermal system should be applied. For ease of review the ingredients searched and utilized to make the IIG determination in the table below is provided in this [Module](#)

JUSTIFICATION OF INGREDIENTS:

(b) (4)

However, the liner should not be applied to the patients' skin as it's designed to protect the patch from the environment and to be discarded before placing the patch on the skin.

An impermeable backing liner made from aluminum coated polyester combined with skin colored polyethylene has been chosen to protect the patch from the environment. The patch is situated on a standard release liner with fluoropolymer-coating. This liner is removed prior to application.

After manufacturing each transdermal patch, together with a cover sheet made of polyethylene terephthalate siliconized on one side, is individually packed into a heat-sealed sachet made of paper / polyethylene terephthalate / aluminum / polyacrylnitrile multilaminate to ensure appropriate protection.

^{(b) (4)}-TDS is composed as shown in the following schematic drawing:

- a cover sheet: siliconized polyethylene terephthalate film
- a backing liner: Polyethylene / thermoplastic resin / aluminum coated polyester film
- an active reservoir layer containing the active pharmaceutical ingredient
- an adhesive matrix layer
- a release liner: fluoropolymer coated polyester film

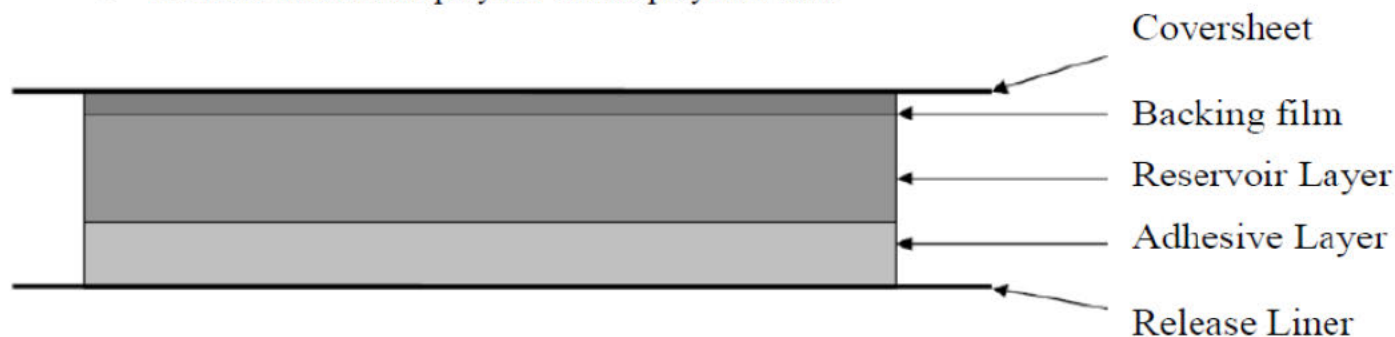


Figure 1 Schematic drawing of newly developed Rivastigmine-TDS

1.1.2 ATTACHMENT 1 – ESTABLISHMENT INFORMATION

Firm, FDA Reg. #	Contact Information
(b) (4)	
Cetero Research (Clinical Study Facility and Clinical Laboratory Facility) 4801 Amber Valley Parkway Fargo, ND 58104 FEI: 3004105783 DUNS Number: 8019670303	Contact: Alan K. Copa, PharmD, Principal Investigator Phone: 701 239-4750 Email: alan.copa@cetero.com

Firm, FDA Reg. #	Contact Information
Cetero Research (Clinical Study Facility) 400 Fountain Lakes Blvd. St. Charles, MO 63301 FEI: 3007245855 DUNS Number: 017378221	Contact: James C. Freeman, MD, Principal Investigator Phone: (701)239-4750 Email: james.freeman@cetero.com
(b) (4)	(b) (4)

Contract Test Laboratory	Details of contact person at contract test laboratories	Proposed Testing
(b) (4)	(b) (4)	(b) (4)



Establishment: Evaluation System

File Edit Search Navigate Options Help Window

ORACLE

Application Drawer

Application Establishments Status Milestones Comments Contacts Product

Application: A 204403/000 Subtype: N/A Sponsor: RILVOGEN INC

Drug Name: RIVASTIGMINE

FEI / CFN	Establishment Name	Profile Code	Last Milestone Name	Last Compliance Date	Status	Date	OAI Alert	FER Re-eval Date
☐ ☐								(b) (4)

Overall Compliance: Date (b) (4), ENDING Recommendation Overall Re-eval Date

OAI Alert Comments

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHANNON L HILL
05/14/2013

MARTIN H Shimer
05/20/2013

Electronic Log Book

Electronic Log Book ID 3598
Contact: Alvogen, Inc.
Contact Person: Jasmine Shah

Reason: Outgoing, FDA Request for
Information
Contact Type: Email

Category: ANDA
ANDA/Control/Protocol #: 204403

FDA Contact: Chitra Mahadevan

Contact Time and Date 4/30/2013 at 2:32:33 PM

Subject: Bioequivalence

Query

Dear Mr. Shah,

I am writing to request a Bioequivalence Telephone Amendment for ANDA 204403, Rivastigmine Transdermal System. In the March 27, 2013 Bioequivalence Dissolution Deficiency Letter, point #2 asks you to "please specify the rotation speed and submit dissolution summary tables for all multimedia dissolution testing." In your April 11, 2013 amendment, you submitted revised multimedia individual unit dissolution data and provided the rotation speed in these tables. However, you did not provide the dissolution summary tables for multimedia dissolution testing. Please submit the multimedia dissolution summary tables, making sure to include the dissolution testing date, electronically as a "Bioequivalence Response to Information Request" no later than 5pm on Tuesday, May 14, 2013.

Please do not hesitate to contact me with any questions/clarification.

Have a nice afternoon.

Kind regards,

Chitra Mahadevan, Pharm.D.
LT, US Public Health Service
Project Manager, Branch 7
Division of Bioequivalence II
Office of Generic Drugs
CDER/FDA

Response

Emailed Mr. Shah on 4/30/2013.

APPEARS THIS WAY ON
ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHITRA MAHADEVAN
04/30/2013

BIOEQUIVALENCE AMENDMENT

ANDA 204403

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810



APPLICANT: Alvogen Pine Brook, Inc.

TEL: (b) (6)

ATTN: Jasmine Shah

FAX: (973) 201-1086

FROM: Chitra Mahadevan

FDA CONTACT PHONE: (240) 276-8817

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on June 12, 2012, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Rivastigmine Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr.

Reference is also made to your amendment dated January 22, 2013.

The Division of Bioequivalence II has completed its review of the submissions referenced above and has identified deficiencies which are presented on the attached ____ page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**

Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence II, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:

*Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810*

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

Please submit your response in electronic format. This will improve document availability to review staff.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

BIOEQUIVALENCE DISSOLUTION DEFICIENCIES

ANDA: 204403

APPLICANT: Alvogen Pine Brook, Inc.

DRUG PRODUCT: Rivastigmine Transdermal System, 4.6 mg/24 hr, 9.5 mg/24 hr, and 13.3 mg/24 hr

The Division of Bioequivalence II (DB II) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The review of the bioequivalence study will be conducted later. The following deficiencies have been identified:

1.

2.

3.

(b) (4)

4. Please provide the Certificate of Analysis (COA) for the 4.6 mg/24 hr (lot #1200BA), 9.5 mg/24 hr (lot # 1401B) and 13.3 mg/24 hr (lot # 2302A) strengths of the reference product.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BARBARA M DAVIT
03/27/2013

ANDA FILING CHECKLIST
(CTD or eCTD FORMAT)
FOR COMPLETENESS AND ACCEPTABILITY of an APPLICATION

ANDA: 204403

APPLICANT: ALVOGEN PINE BROOK, INC.

RELATED APPLICATION(S): NA

DRUG NAME: RIVASTIGMINE TRANSDERMAL SYSTEM

DOSAGE FORM: EXTENDED-RELEASE FILM, 4.6 MG/24 HR AND 9.5 MG/24 HR

LETTER DATE: **JUNE 12, 2012**

RECEIVED DATE: JUNE 12, 2012

- P-IV
- FIRST GENERIC
- EXPEDITED REVIEW REQUEST: **MaPP 5240.1 or MaPP 5240.3** (Approved/Denied)
- PEPFAR
- PET

Electronic or Paper Submission: Gateway Type II DMF# (b) (4)

BASIS OF SUBMISSION:

NDA/ANDA: 22-083

FIRM: NOVARTIS PHARMACEUTICALS CORP.

RLD: EXELON

****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s).**

Review Team:

CHEM Team: DC2 TM 24 ☐ Activity	Bio Team: DBE 2 TM7: Xiaojian Jiang ☒ Activity
RPM: Linda Park ☐ FYI	Bio PM: Chitra Mahadevan ☐ FYI
CHEM RPM: Frank Nice ☐ FYI	Clinical Endpoint Team: (YES) Carol Kim/Nitin Patel ☒ Activity
CHEM Team Leader: Susan Rosencrance ☐ No Assignment Needed in DARRTS	DMF Review Team Leader: ☒ FYI David Skanchy
Labeling Reviewer: Imam, Malik ☐ Activity	Micro Review: (No) ☐ Activity

SPECIAL INSTRUCTIONS FOR DOCUMENT ROOM (applicable only for a response to a refuse to receive):

Regulatory Reviewer: Shannon Hill	Recommendation:
Date: October 22, 2012	☒ FILE ☐ REFUSE to RECEIVE

Comments: EC- 2 YES
 Therapeutic Code: 2013060 DRUGS FOR MEMORY (ALZHEIMERS/SENILITY/DEMENTIA)
 On Cards: YES
 Archival copy: **ELECTRONIC (GATEWAY)**

- For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>
- For a Comprehensive Table of Contents Headings and Hierarchy please go to: <http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf>
- For more CTD and eCTD informational links see the final page of the ANDA Checklist

1. Edit Application Property Type in DARRTS where applicable for

- a. First Generic Received
 Yes No
- b. Market Availability
 Rx OTC
- c. Pepfar
 Yes No
- d. Product Type
 Small Molecule Drug
- e. USP Drug Product (at time of filing review)
 Yes No

2. Edit Submission Patent Records

Yes

3. Edit Contacts Database with Bioequivalence Recordation where applicable

Yes

4. EER (in Draft)

Yes

ADDITIONAL COMMENTS REGARDING THE ANDA:

1. Ask applicant to submit cGMP from Alvogen since they are the applicant and ANDA holder; *received 10/19/2012*
2. Ask applicant for rationale for submitting only 1 month stability data for 2 of the 3 batches of each strength; *Mr. Shah explained that 6 months accelerated stability data is included in this initial submission for 1 batch of each strength and data for remaining batches will be submitted to the agency in the near future.*
3. Spoke with Mr. Jasmine Shah on 10/19/2012

**DIVISION OF CLINICAL REVIEW CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS**

ANDA# 204403 FIRM NAME Alvogen Pine Brook, Inc.

DRUG NAME Rivastigmine Transdermal System, 4.6 mg per 24 hours and 9.5 mg per 24 hours

DOSAGE FORM Transdermal Patch

REFERENCE LISTED DRUG (RLD) Exelon Patch (NDA 022083) 9.5 mg per 24 hours

Requested by: Howard, Eda Date: 6/25/12
Regulatory Support Team, (HFD-615)

Summary of Findings by Division of Clinical Review	
X	Study meets statutory requirements The Division of Clinical Review (DCR) does not require skin irritation/sensitization/adhesion studies for lower strength product (4.6 mg/24 hours). Therefore, the filing review decision regarding the waiver request of the BE study requirement for that strength product is deferred to the DB II. Please see comments to be conveyed to the sponsor.
	Study does NOT meet statutory requirements Reason:
	Waiver meets statutory requirements
	Waiver does NOT meet statutory requirements Reason:

RECOMMENDATION: X COMPLETE INCOMPLETE

Reviewed by:

Reviewer
Carol Y. Kim, Pharm.D.
Clinical Reviewer

Date: _____

John R. Peters, M.D.
Director, Division of Clinical Review

Date: _____

Comments to be conveyed to the sponsor

The data submitted to your application are acceptable for receiving your ANDA. Please note that the acceptability of your data and analyses will be evaluated during the review of the application.

Please include the following additional information for the review:

1. Source documents for each irritation/sensitization score per visit could not be located in case report forms for study C10-1870.
2. The “define.pdf” is incomplete because it did not include detailed description for each code used. As recommended in the OGD Draft Guidance for this product, a detailed description of the codes that are used for each variable in each of the SAS datasets should be included. For example, in a dataset “ds001.xpt”, the code of “L” in variable “F_status” should be defined.
3. “Summary.xpt” dataset has missing information (i.e., it is blank) under variables, “PPIRR”, “PPIRR_RS”, “PPSEN”, and “PPSEN_RS”. For “PPIRR” and “PPSEN”, either “yes” or “no” should be defined for each subject to indicate whether they were included or excluded from the irritation or sensitization analysis. For “PPIRR_RS” and “PPSEN_RS”, reason for exclusion should be defined for each subject.
4. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NOLOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set) for skin irritation/sensitization study. For each subject, include variables to indicate (e.g., yes or no) whether they were included or excluded from the irritation or sensitization analyses.
5. A dataset for eligibility exception (i.e., “ie001”) is blank. Provide complete data.
6. The response (e.g., yes or no) for each inclusion/exclusion criterion for each subject should be provided in SAS .xpt dataset. For example, please see below table for details.

Subject number	Inclusion criterion #1	Inclusion criterion #2	Inclusion criterion #3	
	Yes	Yes	yes	

7. Frequency tables for the following: 1) number of subjects with patch moved and 2) the number of patches moved due to excessive irritation for each treatment group.

MODULE 1: ADMINISTRATIVE

		COMMENT (S)																																			
1.1	1.1.2 Signed and Completed Application Form (356h) (Rx/OTC Status) Rx (original signature) Establishment Information: Yes 1. Drug Substance Manufacturer 2. Drug Product Manufacturer 3. Outside Testing Facility(ies) Establishment information must include the following: ▪ Contact name at the manufacturing site and testing laboratories ▪ US Agent’s name for each site (if applicable) ▪ Address of the manufacturing site for the drug substance and finished product ▪ Address of all outside contract testing laboratories ▪ Phone and fax numbers, email address of contact for each site ▪ Detailed description of function(s) or responsibility(ies) of each site, specify if the function/responsibility is for the Drug Substance, Drug Product or Excipient ▪ CFN/FEI/DUNS number of each site (if available)																																				
1.2	Cover Letter Yes																																				
1.2.1	Form FDA 3674 (PDF) B																																				
*	Table of Contents (paper submission only) N/A																																				
1.3.2	Field Copy Certification (N/A for E-Submissions) N/A (original signature)																																				
1.3.3	Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other: (no qualifying statement) 1. Debarment Certification (original signature) Yes 2. List of Convictions statement (original signature) Yes																																				
1.3.4	Financial Certifications Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) Yes Disclosure Statement (Form FDA 3455) N/A																																				
1.3.5	Patent Information Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations Patent Certification 1. Patent number(s) PIII: 4948807 PIV: 5602176, 6316023 & 6335031 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☒ PIV ☒ (Statement of Notification) ☒ 3. Expiration of Patent(s): 1/8/2019 a. Pediatric exclusivity submitted? N/A b. Expiration of Pediatric Exclusivity? N/A 4. Exclusivity Statement: State marketing intentions? Yes; no unexpired exclusivity Patent and Exclusivity Search Results from query on Appl No 022083 Product 001 in the OB_Rx list. Patent and Exclusivity Search Results from query on Appl No 022083 Product 002 in the OB_Rx list. Patent Data <table border="1" data-bbox="227 1764 1218 2047"> <thead> <tr> <th>Appl No</th> <th>Prod No</th> <th>Patent No</th> <th>Patent Expiration</th> <th>Drug Substance Claim</th> <th>Drug Product Claim</th> <th>Patent Use Code</th> </tr> </thead> <tbody> <tr> <td>N022083</td> <td>001</td> <td>4948807</td> <td>Aug 14, 2012</td> <td>Y</td> <td></td> <td>U - 322</td> </tr> <tr> <td>N022083</td> <td>001</td> <td>5602176</td> <td>Feb 11, 2014</td> <td>Y</td> <td>Y</td> <td>U - 322</td> </tr> <tr> <td>N022083</td> <td>001</td> <td>6316023</td> <td>Jan 8, 2019</td> <td></td> <td>Y</td> <td></td> </tr> <tr> <td>N022083</td> <td>001</td> <td>6335031</td> <td>Jan 8, 2019</td> <td></td> <td>Y</td> <td></td> </tr> </tbody> </table>	Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	N022083	001	4948807	Aug 14, 2012	Y		U - 322	N022083	001	5602176	Feb 11, 2014	Y	Y	U - 322	N022083	001	6316023	Jan 8, 2019		Y		N022083	001	6335031	Jan 8, 2019		Y		
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	U - 322 TREATMENT OF ALZHEIMER'S DEMENTIA Exclusivity Data There is no unexpired exclusivity for this product.											
1.4.1	References Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient Yes b. Type II DMF# (b) (4) c. Type III DMF authorization letter(s) for container closure Yes; (b) (4) 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) Yes; (b) (4) MF (b) (4) RIVASTIGMINE AS MANUFACTURED IN (b) (4) <table border="1"> <tr> <td>Application Status</td> <td>Active</td> </tr> <tr> <td>Status Date</td> <td>08/03/2009</td> </tr> <tr> <td>Status Change Reason</td> <td></td> </tr> <tr> <td>Holder Name & Address</td> <td>(b) (4)</td> </tr> <tr> <td>MF Type</td> <td>Type II</td> </tr> </table>	Application Status	Active	Status Date	08/03/2009	Status Change Reason		Holder Name & Address	(b) (4)	MF Type	Type II	
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Status Date	08/03/2009											
Status Change Reason												
Holder Name & Address	(b) (4)											
MF Type	Type II											
1.12.4	Request for Comments and Advice - Proprietary name requested No If Yes, did the firm provide the request as a separate electronic amendment labeled "Proprietary Name Request" at initial time of filing 1. Yes N/A 2. No - contact the firm to submit the request as a separate electronic amendment.											
1.12.11	Basis for Submission NDA#: 22-083 Ref Listed Drug: EXELON Firm: NOVARTIS PHARMACEUTICALS CORP. ANDA suitability petition required? N/A If Yes, provide petition number and copy of approved petition ANDA Citizen's Petition Required? N/A If Yes, provide petition number and copy of petition											
1.12.12	Comparison between Generic Drug and RLD-505(j)(2)(A) 1. Conditions of use Same as RLD 2. Active ingredients Same as RLD 3. Inactive ingredients Justified 4. Route of administration Same as RLD 5. Dosage Form Same as RLD 6. Strength Same as RLD											
1.12.14	Environmental Impact Analysis Statement (cite 21CFR 25.31, if applicable) Yes											
1.12.15	Request for Waiver Request for Waiver of In-Vivo BA/BE Study(ies) Yes	on 4.6 mg/24 hr										
1.14.1	Draft Labeling (Multi Copies N/A for E-Submissions) 1.14.1.1 4 copies of draft for paper submission only (each strength and container) Yes 1.14.1.2 1 side by side labeling comparison of containers and carton with all differences visually highlighted and annotated Yes 1.14.1.3 1 package insert (content of labeling) and SPL submitted											

	electronically Yes HOW SUPPLIED: Rivastigmine Patch 4.6 mg/24 hours Each patch of 4.6 cm² contains 6.9 mg rivastigmine with <i>in-vivo</i> release rate of 4.6 mg/24 hours. Carton of 30.....NDC (b) (4) Rivastigmine Patch 9.5 mg/24 hours Each patch of 9.2 cm² contains 13.8 mg rivastigmine with <i>in-vivo</i> release rate of 9.5 mg/24 hours. Carton of 30.....NDC (b) (4)	
1.14.3	Listed Drug Labeling 1.14.3.1 1 side by side labeling (package and patient insert) comparison with all differences visually highlighted and annotated Yes 1.14.3.3 RLD package insert, 1 RLD label and 1 RLD container label Yes	

MODULE 2: Quality Overall Summary

		COMMENT (S)
2.3	Quality Overall Summary (QOS) E-Submission: PDF Yes Word Processed e.g., MS Word Yes A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ Question based Review (QbR) Yes 2.3.S Drug Substance (Active Pharmaceutical Ingredient) Yes 2.3.S.1 General Information 2.3.S.2 Manufacture 2.3.S.3 Characterization 2.3.S.4 Control of Drug Substance 2.3.S.5 Reference Standards or Materials 2.3.S.6 Container Closure System 2.3.S.7 Stability 2.3.P Drug Product Yes 2.3.P.1 Description and Composition of the Drug Product 2.3.P.2 Pharmaceutical Development 2.3.P.2.1 Components of the Drug Product 2.3.P.2.1.1 Drug Substance 2.3.P.2.1.2 Excipients 2.3.P.2.2 Drug Product Oral Solids: Immediate Release or Modified Release (Matrix Technology or Compressed Film Coated Components) tablet scoring data per Draft <i>Guidance for Industry, Tablet Scoring: Nomenclature, Labeling and Data for Evaluation</i> (if applicable) 2.3.P.2.3 Manufacturing Process Development 2.3.P.2.4 Container Closure System 2.3.P.3 Manufacture 2.3.P.4 Control of Excipients 2.3.P.5 Control of Drug Product 2.3.P.6 Reference Standards or Materials 2.3.P.7 Container Closure System 2.3.P.8 Stability	

MODULE 2.7: Clinical Summary

		COMMENT (S)																		
2.7	Clinical Summary (Bioequivalence) Model BE Data Summary Tables E-Submission: PDF Yes Word Processed: e.g., MS Word Select 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods 2.7.1.1 Background and Overview Table 1. Submission Summary Yes Table 4. Bioanalytical Method Validation Yes Table 6. Formulation Data Yes Table 10. Study Information Table 11. Product Information 2.7.1.2 Summary of Results of Individual Studies Table 5. Summary of In Vitro Dissolution Yes (include complete comparative In Vitro Dissolution Data (individual) with Certificate of Analysis [CoA] for Test and Reference products including: potency, assay, content uniformity, date of manufacture and lot number) Table 9. Reanalysis of Study Samples Table 12. Dropout Information Table 13. Protocol Deviation Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analysis 2.7.1.3 Comparison and Analyses of Results Across Studies Table 2. Summary of Bioavailability (BA) Studies Yes Table 3. Statistical Summary of the Comparative BA Data Yes Table 3 Statistical Summary of the Comparative Data Table 3.1 Irritation Analysis, PPPI <table border="1" data-bbox="245 1129 1248 1314"> <thead> <tr> <th colspan="3">Rivastigmine Transdermal System, 4.6 mg/ 24 Hours (Study No. C10-1870, S11-0069, R10-1318) N=262¹</th> </tr> <tr> <th>Variable</th> <th>A-1.25B</th> <th>Upper Bound of One-Sided 95% Confidence Limit</th> </tr> </thead> <tbody> <tr> <td>Cumulative Irritation Scores (Dermal Response + Other Effect Scores) (Test – 1.25*Reference)</td> <td>-8.60592</td> <td>-7.82006</td> </tr> </tbody> </table> ¹Subjects used in statistical analysis for PPPI Table 3.2 Irritation Analysis, PPPS <table border="1" data-bbox="245 1409 1248 1593"> <thead> <tr> <th colspan="3">Rivastigmine Transdermal System, 4.6 mg/ 24 Hours (Study No. C10-1870, S11-0069, R10-1318) N=228²</th> </tr> <tr> <th>Variable</th> <th>A-1.25B</th> <th>Upper Bound of One-Sided 95% Confidence Limit</th> </tr> </thead> <tbody> <tr> <td>Cumulative Irritation Scores (Dermal Response + Other Effect Scores) (Test – 1.25*Reference)</td> <td>-0.85239</td> <td>-0.73758</td> </tr> </tbody> </table> ²Subjects used in statistical analysis for PPPS	Rivastigmine Transdermal System, 4.6 mg/ 24 Hours (Study No. C10-1870, S11-0069, R10-1318) N=262 ¹			Variable	A-1.25B	Upper Bound of One-Sided 95% Confidence Limit	Cumulative Irritation Scores (Dermal Response + Other Effect Scores) (Test – 1.25*Reference)	-8.60592	-7.82006	Rivastigmine Transdermal System, 4.6 mg/ 24 Hours (Study No. C10-1870, S11-0069, R10-1318) N=228 ²			Variable	A-1.25B	Upper Bound of One-Sided 95% Confidence Limit	Cumulative Irritation Scores (Dermal Response + Other Effect Scores) (Test – 1.25*Reference)	-0.85239	-0.73758	
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Cumulative Irritation Scores (Dermal Response + Other Effect Scores) (Test – 1.25*Reference)	-0.85239	-0.73758																		

Table 3.3 Bioavailability Results for R10-1307

Bioavailability and Adhesion Study (R10-1307) Rivastigmine Transdermal Patch, 9.5 mg/24 Hour 9.5 mg/24 Hour (1 x 9.5 mg/24 Hour Patch) Geometric Means ¹ , Ratio of Means, and 90% Confidence Intervals Ln-Transformed Data Rivastigmine N=27 ²				
Parameter	Test	Reference	% Ratio	90% C.I.
AUC _{0-t}	163464.95	143876.95	113.61	(106.60, 121.09)
AUC _{0-inf}	164334.80	144824.77	113.47	(106.50, 120.90)
C _{max}	9067.37	7869.17	115.23	(107.05, 124.02)

¹Geometric means are based on exponential of least squares means of ln-transformed values
²Subjects used in final statistical results

Table 3.4 Statistical Summary of the Comparative Adhesion Data – Wilcoxon Signed Rank Test and 95% Bootstrap

Bioavailability and Adhesion Study (R10-1307) Rivastigmine Transdermal Patch, 9.5 mg/24 Hour 9.5 mg/24 Hour (1 x 9.5 mg/24 Hour Patch) Wilcoxon Signed Rank Test and Summary of 95% Bootstrapping Confidence Limit using CAS PPPA Population Rivastigmine N=27 ¹				
Variable	Wilcoxon Signed Rank Test		95% Bootstrap	
	Test Statistic	p Value	Median Difference	Upper Bound of 95% Bootstrap Confidence Limit of the Median Difference
Cumulative Adhesion Scores (Test – 1.25* Reference)	-149.5	0.2004	0.0	0.00

¹Subjects used in the PPPA for Adhesion analysis

Table 16. Composition of Meal Used in Fed Bioequivalence Study N/A
(if the standard meal referenced in the CDER Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies is used, then provide a statement of compliance to the FDA standard meal. If an alternative meal is used, then complete the summary table with the name of the food item(s), ingredient(s), amount (g), energy (kcal), protein (kcal), fat (kcal) and carbohydrates (kcal).

2.7.1.4 Appendix

Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples

2.7.4.1.3 Demographic and Other Characteristics of Study Population

Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study Yes

2.7.4.2.1.1 Common Adverse Events

Table 8. Incidence of Adverse Events in Individual Studies Yes

MODULE 3: 3.2.S DRUG SUBSTANCE

		COMMENT (S)
3.2.S.1	General Information) Yes (Do not refer to DMF) 3.2.S.1.1 Nomenclature 3.2.S.1.2 Structure 3.2.S.1.3 General Properties	
3.2.S.2	Manufacturer Drug Substance (Active Pharmaceutical Ingredient) Must correlate to the establishment information submitted in annex to Form FDA 356h. 1. Name and Full Address(es)of the Facility(ies) Yes 2. Contact name, phone and fax numbers, email address Yes 3. U.S Agent’s name (if applicable) Yes 4. Specify Function or Responsibility Yes 5. Type II DMF number for API Yes 6. CFN, FEI or DUNS numbers (if available) Yes	

Manufacturing and Testing Site	(b) (4)
Address:	
Responsibility	Manufacturing, testing, packing, labeling, release and storage of Rivastigmine
Contact Person:	(b) (4)
Phone No.	
Fax No.	
E-mail	
FEI Number	
DUNS	

US Agent	(b) (4)
Address:	
Responsibility	
Contact Person:	
Phone No.	
Fax No.	
E-mail	

The drug substance, Rivastigmine, manufactured by (b) (4) is consistent with the procedures and controls described in Drug Master File (DMF) No. (b) (4) on file with FDA.

3.2.S.3

Characterization Yes
 Provide the following in tabular format:
 1. Name of Impurity(ies)
 2. Structure of Impurity(ies)
 3. Origin of Impurity(ies)

3.2.S.4

Control of Drug Substance (Active Pharmaceutical Ingredient)
3.2.S.4.1 Specification
 Testing specifications and data from drug substance manufacturer(s) Yes
3.2.S.4.2 Analytical Procedures Yes
3.2.S.4.3 Validation of Analytical Procedures
 (API that is USP or reference made to DMF, must provide verification of USP or DMF procedures) N/A
 1. Spectra and chromatograms for reference standards and test samples Yes
 2. Samples-Statement of Availability and Identification of:
 a. Drug Substance Yes
 b. API lot number(s)

3.2.S.4.3 Samples – Statement of Availability and Identification (Rivastigmine)

 As per 21 CFR 314.50(e), samples of the following are available on-site at (b) (4)
 (b) (4) Samples will be supplied upon request by the Agency. The drug substance (Rivastigmine) utilized in the manufacture of the exhibit lot of Rivastigmine Transdermal System, 4.6 mg/24hr and 9.5 mg/24hr and the reference standards utilized to test the drug substance are identified in the tables below.

Drug Substance	
Manufacturer	Batch #
A11222A	(b) (4)
	001110-000

3.2.S.4.4 Batch Analysis
 1. COA(s) specifications and test results from drug substance mfg(s) Yes
 2. Applicant certificate of analysis Yes
3.2.S.4.5 Justification of Specification Yes

3.2.S.5	Reference Standards or Materials (Do not refer to DMF) Yes	
3.2.S.6	Container Closure Systems N/A; refer to DMF # (b) (4)	
3.2.S.7	Stability 1. Retest date or expiration date of API N/A; refer to DMF # (b) (4)	

MODULE 3: 3.2.P DRUG PRODUCT

		COMMENT (S)														
3.2.P.1	Description and Composition of the Drug Product - Unit composition with indication of the function of the inactive ingredient(s) Yes - Inactive ingredients and amounts are appropriate per IIG (per/dose justification) Yes - Conversion from % to mg/dose values for inactive ingredients (if applicable) N/A - Elemental iron: provide daily elemental iron calculation or statement of adherence to 21CFR73.1200 (calculation of elemental iron intake based on maximum daily dose (MDD) of the drug product is preferred if this section is applicable) N/A - Injections: If the reference listed drug is packaged with a drug specific diluent then the diluent must be Q1/Q2 and must be provided in the package configuration N/A															
3.2.P.2	Pharmaceutical Development Pharmaceutical Development Report Yes															
3.2.P.3	Manufacture 3.2.P.3.1 Drug Product Must correlate to the establishment information submitted in annex to Form FDA 356h for the finished dosage manufacturer and all outside contract testing laboratories. - Name and Full Address(es) of the Facility(ies) Yes - Contact name, phone and fax numbers, email address Yes - U.S Agent's name (if applicable) No - Specify Function or Responsibility Yes - CGMP Certification (from both applicant and drug product manufacturer if different entities) Select - CFN, FEI or DUNS numbers (if available) Yes Alvogen Pine Brook, Inc. is the ANDA holder and will be distributing the product. (b) (4) (b) (4) is used as a contractor to perform all of the manufacturing, packaging, testing and stability testing functions of the drug product. Additionally, the microbiological tests for the finished product release and stability testing is performed by (b) (4) (b) (4) The drug product, Rivastigmine Transdermal System, 4.6 mg/24hr and 9.5 mg/24hr, will be manufactured, tested, packaged and labeled at the following facility: <table border="1"> <tr> <td>Manufacturing and Testing Site</td> <td>(b) (4)</td> </tr> <tr> <td>Address</td> <td>(b) (4)</td> </tr> <tr> <td>Responsibility</td> <td> - Drug substance and finished product analytical testing and release. - Inactive ingredients and packaging components analytical testing and release. - Finished product pharmaceutical manufacturing, packaging and labeling. - Intermediate, finished product and stability testing. - Finished product storage. </td> </tr> <tr> <td>Contact Person</td> <td>(b) (4)</td> </tr> <tr> <td>Establishment Registration No.</td> <td>Registration is pending</td> </tr> <tr> <td>DUNS No.</td> <td>(b) (4)</td> </tr> <tr> <td>Fax No.</td> <td>(b) (4)</td> </tr> </table>	Manufacturing and Testing Site	(b) (4)	Address	(b) (4)	Responsibility	- Drug substance and finished product analytical testing and release. - Inactive ingredients and packaging components analytical testing and release. - Finished product pharmaceutical manufacturing, packaging and labeling. - Intermediate, finished product and stability testing. - Finished product storage.	Contact Person	(b) (4)	Establishment Registration No.	Registration is pending	DUNS No.	(b) (4)	Fax No.	(b) (4)	
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Responsibility	- Drug substance and finished product analytical testing and release. - Inactive ingredients and packaging components analytical testing and release. - Finished product pharmaceutical manufacturing, packaging and labeling. - Intermediate, finished product and stability testing. - Finished product storage.															
Contact Person	(b) (4)															
Establishment Registration No.	Registration is pending															
DUNS No.	(b) (4)															
Fax No.	(b) (4)															

Contract Test Laboratory	Details of contact person at contract test laboratories	Proposed Testing
(b) (4)	(b) (4)	1. Microbiological testing of the finished product
3.2.P.3.2 Batch Formula Yes 3.2.P.3.3 Description of Manufacturing Process and Process Controls 1. Description of the Manufacturing Process Yes 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified Yes 3. Master packaging records for intended marketing container(s) Yes 4. If sterile product N/A 5. Reprocessing Statement (cite 21CFR 211.115, submitted by the drug product manufacturer and the applicant, if different entities) Yes 3.2.P.3.4 Controls of Critical Steps and Intermediates Yes 3.2.P.3.5 Process Validation and/or Evaluation 1. Microbiological sterilization validation N/A 2. Filter validation (if aseptic fill) N/A Proposed Commercial Batch Size: 4.6 mg/24 hr: (b) (4) (ANDA batch size is (b) (4)) 9.5 mg/24 hr: (b) (4) (ANDA batch size is (b) (4))		
3.2.P.4	Controls of Excipients (Inactive Ingredients) Source of inactive ingredients identified Yes 3.2.P.4.1 Specifications 1. Testing specifications (including identification and characterization) Yes 2. Suppliers' COA (specifications and test results) Yes 3.2.P.4.2 Analytical Procedures USP/NF 3.2.P.4.3 Validation of Analytical Procedures N/A 3.2.P.4.4 Justification of Specifications: 1. Applicant COA Yes	

MODULE 3: 3.2.P DRUG PRODUCT (Continued)

	COMMENT (S)
3.2.P.5 Controls of Drug Product 3.2.P.5.1 Specification(s) Yes 3.2.P.5.2 Analytical Procedures Yes 3.2.P.5.3 Validation of Analytical Procedures (if using USP procedure, must provide verification of USP procedure) N/A Samples - Statement of Availability and Identification of: 1. Finished Dosage Form Yes 2. Lot number(s) and strength of Drug Product(s)	

3.2.P.5.3 Samples – Statement of Availability and Identification

As per 21 CFR 314.94(a)(10), samples need not be submitted until requested by FDA. Samples of the following are available, and will be supplied upon Agency’s request.

Rivastigmine Transdermal System, 4.6 mg/24 hr and 9.5 mg/24 hr

Product	Lot/Batch #
Rivastigmine Transdermal System, 4.6 mg/24 hr	C0002AL0AT ¹
	C0006AL0AT
	C0010AL0AT
Rivastigmine Transdermal System, 9.5 mg/24 hr	C0004AL0AU ²
	C0008AL0AU
	C0012AL0AU

(1) Batch C0002AL0AT was utilized for the Skin Irritation and Sensitization Study.

(2) Batch C004AL0AU was utilized for the Bioequivalence and Adhesion Study.

3.2.P.5.4 Batch Analysis

Certificate of Analysis for Finished Dosage Form Yes

3.2.P.5.5 Characterization of Impurities Yes

3.2.P.5.6 Justification of Specifications Yes

3.2.P.7 Container Closure System

- 1. Summary of Container/Closure System (if new resin, provide data) Yes
- 2. Components Specification and Test Data Yes
- 3. Packaging Configuration and Sizes Yes
- 4. Container/Closure Testing (recommended additional testing for all plastic)N/A
 - a. Solid Orals: water permeation, light transmissionN/A
 - b. Liquids: leachables, extractables, light transmissionN/A
- 5. Source of supply and suppliers address Yes

3.2.P.8 3.2.P.8.1 Stability (Finished Dosage Form)

- 1. Stability Protocol submitted Yes
 - 2. Expiration Dating Period 24 months
- 3.2.P.8.2 Post-approval Stability and Conclusion**
Post Approval Stability Protocol and Commitments Yes

3.2.P.8.3 Stability Data

- 1. Accelerated stability data
 - a. four (4) time points 0,1,2,3 Yes

-OR-

 - b. three (3) time points 0,3,6 (if 3 time points for accelerated stability data are submitted then provide 3 exhibit batches along with 12 months of room temperature stability data –Refer to Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products November 2003, Section B) N/A
2. Batch numbers on stability records the same as the test batch Yes;

C0002AL0AT

C0004AL0AU

Conclusion

This stability conclusion is based on current stability data of the batches C0002AL0AT and C0004AL0AU up to 6 months of storage and batch C0006AL0AT, C0008AL0AU, C0010AL0AT and C0012AL0AU up to 1 month of storage, representing the dosage strengths 4.6 mg/24 hr and 9.5 mg/24 hr.

MODULE 3: 3.2.R REGIONAL INFORMATION (Drug Substance)

		COMMENT (S)
3.2.R Drug Substance	3.2.R.1.S Executed Batch Records for drug substance (if available) N/A 3.2.R.2.S Comparability Protocols N/A 3.2.R.3.S Methods Validation Package Yes Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs)	

MODULE 3: 3.2.R REGIONAL INFORMATION (Drug Product)

		COMMENT (S)
3.2.R Drug Product	3.2.R.1.P.1 Executed Batch Records Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) 3.2.R.1.P.1 Executed Batch Records  (b) (4)	

Bulk Package Reconciliation required if bulk packaging is used to achieve the minimum package requirement. Provide the following information in their respective sections:

- a. Bulk Package Label (1.14.1) N/A
- b. Bulk Package Stability (accelerated stability data [0,1,2,3] –**OR**- room temperature [0,3,6]) (3.2.P.8) N/A
- c. Bulk Package Container and Closure information (3.2.P.7) N/A

3.2.R.1.P.2 Information on Components Yes

3.2.R.2.P Comparability Protocols N/A

3.2.R.3.P Methods Validation Package Yes

Methods Validation Package (3 copies for paper and N/A for E-Submissions)

(Required for Non-USP drugs)

MODULE 5: CLINICAL STUDY REPORTS

		COMMENT (S)
5.2	Tabular Listing of Clinical Studies Yes	
5.3.1 (complete study data)	Bioavailability/Bioequivalence 1. Formulation data same? a. Comparison of all Strengths (proportionality of multiple strengths) Yes b. Parenterals, Ophthalmics, Otics and Topicals (21 CFR 314.94 (a)(9)(iii)-(v) N/A 2. Lot Numbers and strength of Products used in BE Study(ies) ANDA: C0002A10AT RLD: 1200BA 3. Study Type: IN-VIVO PK STUDY(IES) (Continue with the appropriate study type box below)	
	See Module 2.7 Clinical Summary for placement of BA/BE Summary for tables 9 – 16. The study data that support the BA/BE summary tables should be provided in the corresponding sections below: 5.3.1.2 Comparative BA/BE Study Reports 5.3.1.3 In Vitro-In-Vivo Correlation Study Reports (exception: all dissolution data should be placed in 2.7) 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies Case Report Forms should be placed under the study to which they pertain, and appropriately tagged. Refer to The eCTD Backbone File Specification for Study Tagging //www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf	
5.4	Literature References	

	Possible Study Types:	
Study Type	IN-VIVO BE STUDY(IES) with PK ENDPOINTS (i.e., fasting/fed/sprinkle) 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) Select 2. EDR Email: Data Files Submitted Select 3. In-Vitro Dissolution Select	
Study Type	IN-VIVO BE STUDY with CLINICAL ENDPOINTS 1. Properly defined BE endpoints (eval. by Clinical Team) Select 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80,1.25) Select 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) Select 4. EDR Email: Data Files Submitted Select	
Study Type	IN-VITRO BE STUDY(IES) (i.e., in vitro binding assays) Select 1. Study(ies) meets BE criteria (90% CI of 80-125) Select 2. EDR Email: Data Files Submitted Select 3. In-Vitro Dissolution Select	
Study Type	NASALLY ADMINISTERED DRUG PRODUCTS 1. Solutions (Q1/Q2 sameness) Select a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) Select 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study Select 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) Select 2. EDR Email: Data Files Submitted Select b. In-Vivo BE Study with Clinical End Points Select 1. Properly defined BE endpoints (eval. by Clinical Team) Select 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) Select 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) Select 4. EDR Email: Data Files Submitted Select c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) Select	
Study Type	IN-VIVO BE STUDY(IES) with PD ENDPOINTS (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) Select 2. Pivotal Study (study meets BE criteria 90%CI of 80-125) Select	
Study Type	TRANSDERMAL DELIVERY SYSTEMS 1. In-Vivo PK Study Yes a. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) Yes b. In-Vitro Dissolution Yes c. EDR Email: Data Files Submitted Select 2. Adhesion Study Yes 3. Skin Irritation/Sensitization Study Yes	

Updated 5/1/2012

Active Ingredient Search - Windows Internet Explorer
 http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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Active Ingredient Search Results from "OB_Rx" table for query on "rivastigmine."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N022083		No	RIVASTIGMINE	FILM, EXTENDED RELEASE; TRANSDERMAL	13.3MG/24HR	EXELON	NOVARTIS
N022083		No	RIVASTIGMINE	FILM, EXTENDED RELEASE; TRANSDERMAL	4.6MG/24HR	EXELON	NOVARTIS
N022083		Yes	RIVASTIGMINE	FILM, EXTENDED RELEASE; TRANSDERMAL	9.5MG/24HR	EXELON	NOVARTIS
A091689	AB	No	RIVASTIGMINE TARTRATE	CAPSULE; ORAL	EQ 1.5MG BASE	RIVASTIGMINE TARTRATE	ALEMBIC PHARMS LTD
A091689	AB	No	RIVASTIGMINE TARTRATE	CAPSULE; ORAL	EQ 3MG BASE	RIVASTIGMINE TARTRATE	ALEMBIC PHARMS LTD
A091689	AB	No	RIVASTIGMINE TARTRATE	CAPSULE; ORAL	EQ 4.5MG BASE	RIVASTIGMINE TARTRATE	ALEMBIC PHARMS LTD
A091689	AB	No	RIVASTIGMINE TARTRATE	CAPSULE; ORAL	EQ 6MG BASE	RIVASTIGMINE TARTRATE	ALEMBIC PHARMS LTD
A077130	AB	No	RIVASTIGMINE TARTRATE	CAPSULE; ORAL	EQ 1.5MG BASE	RIVASTIGMINE TARTRATE	DR REDDYS LABS INC
A077130	AB	No	RIVASTIGMINE TARTRATE	CAPSULE; ORAL	EQ 3MG BASE	RIVASTIGMINE TARTRATE	DR REDDYS LABS INC
A077130	AB	No	RIVASTIGMINE TARTRATE	CAPSULE; ORAL	EQ 4.5MG BASE	RIVASTIGMINE TARTRATE	DR REDDYS LABS INC

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Orange Book Detail Record Search - Windows Internet Explorer

http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=022083&TABLE1=OB_Rx

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FDA Home Drug Databases Orange Book

Search results from the "OB_RX" table for query on "022083."

Active Ingredient:	RIVASTIGMINE
Dosage Form;Route:	FILM, EXTENDED RELEASE; TRANSDERMAL
Proprietary Name:	EXELON
Applicant:	NOVARTIS
Strength:	4.6MG/24HR
Application Number:	N022083
Product Number:	001
Approval Date:	Jul 6, 2007
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	RIVASTIGMINE
Dosage Form;Route:	FILM, EXTENDED RELEASE; TRANSDERMAL
Proprietary Name:	EXELON
Applicant:	NOVARTIS
Strength:	9.5MG/24HR
Application Number:	N022083
Product Number:	002
Approval Date:	Jul 6, 2007
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	

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Patent and Exclusivity Search Results - Windows Internet Explorer

http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexdnew.cfm?Appl_No=022083&Product_No=001&table1=OB_Rx

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Patent and Exclusivity Search Results from query on Appl No 022083 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N022083	001	4948807	Aug 14, 2012	Y		U - 322	
N022083	001	5602176	Feb 11, 2014	Y	Y	U - 322	
N022083	001	6316023	Jan 8, 2019		Y		
N022083	001	6335031	Jan 8, 2019		Y		

Exclusivity Data

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be respect to other claims which may apply.

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Patent and Exclusivity Search Results - Windows Internet Explorer

http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexdnew.cfm?Appl_No=022083&Product_No=002&table1=OB_Rx

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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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Patent and Exclusivity Search Results from query on Appl No 022083 Product 002 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N022083	002	4948807	Aug 14, 2012	Y		U - 322	
N022083	002	5602176	Feb 11, 2014	Y	Y	U - 322	
N022083	002	6316023	Jan 8, 2019		Y		
N022083	002	6335031	Jan 8, 2019		Y		

Exclusivity Data

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not respect to other claims which may apply.

[View a list of all patent use codes](#)

[View a list of all exclusivity codes](#)

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Application Drawer

Application Establishments Status Milestones Comments Contacts Product

Application: A 204403/000 Subtype: R/A Sponsor: ALVOGEN INC
 Drug Name: RIVASTIGMINE

FEI / CFN	Establishment Name	Profile Code	Last Milestone Name	Last Compliance Date	Status	Date	OAI Alert	EER Re-eval Date
(b) (4)								

Overall Compliance: Date (b) (4) Recommendation PENDING Overall Re-eval Date

OAI Alert Comments

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHANNON L HILL
11/13/2012

MARTIN H Shimer
11/19/2012



ANDA 204403

Alvogen Pine Brook, Inc.
Attention: Jasmine Shah
10 Bloomfield Avenue
Building B
Pine Brook, NJ 07058

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Since your ANDA is received prior to Oct. 1, 2012, you must pay the backlog fee, per GDUFA. In addition, you will be obliged to pay other fees according to GDUFA on or after Oct. 1, 2012, including facility fees and, if appropriate, drug master file (DMF) fees. If you fail to pay any of these fees within the allotted time, the Agency may take appropriate action, per GDUFA, to not receive future generic drug submissions or classify products as misbranded at facilities that failed to pay the facility fee. Please refer to <http://www.fda.gov/gdufa> website for more information about GDUFA.

Reference is also made to the telephone conversation dated October 19, 2012 and your correspondence dated October 19, 2012.

NAME OF DRUG: Rivastigmine Transdermal System Extended-release Film,
4.6 mg/24 hr and 9.5 mg/24 hr

DATE OF APPLICATION: June 12, 2012

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 12, 2012

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:
 - 1) Each owner of the patent or the representative designated by the owner to receive the notice;
 - 2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.
 - 3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).
- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.
- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.
- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide

a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (240) 276-8675.

We will correspond with you further after we have had the opportunity to review the application.

Please include the following additional information for the review:

1. Source documents for each irritation/sensitization score per visit could not be located in case report forms for study C10-1870.
2. The "define.pdf" is incomplete because it did not include detailed description for each code used. As recommended in the OGD Draft Guidance for this product, a detailed description of the codes that are used for each variable in each of the SAS datasets should be included. For example, in a dataset "ds001.xpt", the code of "L" in variable "F_status" should be defined.
3. "Summary.xpt" dataset has missing information (i.e., it is blank) under variables, "PPIRR", "PPIRR_RS", "PPSEN", and "PPSEN_RS". For "PPIRR" and "PPSEN", either "yes" or "no" should be defined for each subject to indicate whether they were included or excluded from the irritation or sensitization analysis. For "PPIRR_RS" and "PPSEN_RS", reason for exclusion should be defined for each subject.
4. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NOLOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set) for skin irritation/sensitization study. For each subject, include variables to indicate (e.g., yes or no) whether they were included or excluded from the irritation or sensitization analyses.
5. A dataset for eligibility exception (i.e., "ie001") is blank. Provide complete data.
6. The response (e.g., yes or no) for each inclusion/exclusion criterion for each subject should be provided in SAS .xpt dataset. For example, please see below table for details.

Subject number	Inclusion criterion#1	Inclusion criterion#2	Inclusion criterion#3

	Yes	Yes	Yes

7. Frequency tables for the following: 1) number of subjects with patch moved and 2) the number of patches moved due to excessive irritation for each treatment group.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Linda Park
Regulatory Project Manager
240-276-8536

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTIN H Shimer
11/19/2012
Signing for Wm Peter Rickman



ANDA See Attached

Date: 8/20/2012

Attention:
Department of Regulatory Affairs
ALVOGEN INC
10 BLOOMFIELD AVE BLDG B STE 2
PINE BROOK, NJ 07058

RE: Request to Withdraw Applications from the Generic Drug Backlog to Avoid Incurring Backlog Fee

Dear Sir or Madam:

This letter is in reference to your Abbreviated New Drug Applications (ANDAs), included in the attached list, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III), enacted on July 9, 2012, establish a one-time backlog fee for any ANDA that is pending at the US Food and Drug Administration (FDA) on October 1, 2012 and has not received a tentative approval.

FDA is issuing this letter to encourage applicants who have pending ANDAs for which the applicants no longer wish to seek approval to notify FDA of the request to withdraw those ANDAs (see Federal Register Notice Docket Number FDA-2012-N-0879). **Requests for withdrawal should be submitted in writing individually for each ANDA as a "Request for Withdrawal" to the affected ANDA.** A decision to withdraw the ANDA is without prejudice to refile.

Any ANDA that is not withdrawn by September 28, 2012 will incur the obligation to pay the backlog fee. Payment of backlog fees will be due no later than 30 calendar days after publication in the Federal Register of a notice (to be issued by October 31, 2012) announcing the amount of the backlog fee. Applicants with original ANDAs that fail to pay the backlog fee by the due date will be placed on a publicly available arrears list, and FDA will not receive new ANDAs or supplements submitted by those applicants, or any affiliates of those applicants, until the outstanding fee is paid.

To avoid incurring the backlog fee for an application, you, the applicant, must submit a request to withdraw the application and that request must be received by the FDA on or before **September 28, 2012**. However, to expedite this process, you are encouraged to submit the request by **September 15, 2012**.

You should submit the request to withdraw your applications by standard application submission methods. If an application was submitted via the FDA electronic gateway, a request for withdrawal should be submitted to the application via the gateway. Alternatively, you should send written notification to the ANDA archival file at the following address: Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Document Control Room, Metro Park North VII, 7620 Standish Pl., Rockville, MD 20855.

In addition, please provide electronic confirmation of all ANDAs you wish to withdraw by sending an email to OGDGDUFA@fda.hhs.gov within the timeframe specified above.

For your convenience, a list of pending ANDAs for which we have identified you as the applicant is attached. **However, this list may be incomplete. Therefore, it is important to note that the absence of an ANDA from this list does not exempt that ANDA from incurring a backlog fee. Please verify the list for completeness of all ANDAs you have submitted. Discrepancies should be reported to the email address noted above.**

The GDUFA statute exempts only generic Positron Emission Tomography (PET) products from the user fees. There are no additional exemptions or waivers for GDUFA fees beyond those in the statute.

If you have questions regarding this communication, contact Thomas Hinchliffe at OGDGDUFA@fda.hhs.gov.

Please direct general GDUFA questions to ASKGDUFA@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: Attached List of ANDAs

PENDING ANDAs
(List produced as of 8/20/2012)

<u>ANDA #</u>	<u>Drug Name</u>
204291	CARBIDOPA
65515	DOXORUBICIN HYDROCHLORIDE
	(b) (4)
204621	NEVIRAPINE
203924	PRIMAQUINE PHOSPHATE
204403	RIVASTIGMINE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CECELIA M PARISE
08/24/2012

PK Study #R10-1307; 9.5 mg/24 hr

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			5.3.1.2.4. Protocol or Amendment (protocol.pdf)
Assay Methodology	☒	☐			5.3.1.4.25.3.2. Analysis Program (bioanalytical-study-report.pdf)
Procedure SOP	☒	☐			5.3.1.4.25.3.2. Analysis Program (bioanalytical-study-report.pdf) 5.3.1.4.25.3.2. Analysis Program (analyt-validation.pdf)
Methods Validation	☒	☐			5.3.1.4.25.3.2. Analysis Program (analyt-validation.pdf)
Study Results Ln/Lin	☒	☐			5.3.1.2.3. Study Report Body (report-body.pdf)
Adverse Events	☒	☐			5.3.1.2.22 Adverse Event Listings (list-adverse-events.pdf)
IRB Approval	☒	☐			5.3.1.2.6. IEC IRB Consent Form List (iec-irb-list.pdf)
Dissolution Data	☒	☐			1.12.12. Comparison of Generic Drug and Reference Listed Drug (compare-disso-data.pdf) 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods (dbe-table-5.pdf) 3.2.P.2. Pharmaceutical Development (pharma-development.pdf)
Pre-screening of Patients	☒	☐			5.3.1.2.3. Study Report Body (report-body.pdf)
Chromatograms	☒	☐			5.3.1.4.25.3.2. Analysis Program (bioanalytical-study-report.pdf)
Consent Forms	☒	☐			5.3.1.2.6. IEC IRB Consent Form List (iec-irb-list.pdf)
Composition	☒	☐			2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods (dbe-table-6.pdf)

					3.2.P.1. Description and Composition of the Drug Product (desc-and-comp-fp.pdf)
Summary of Study	☒	☐			5.3.1.2.2. Synopsis (synopsis.pdf)
Individual Data & Graphs, Linear & Ln	☒	☐			5.3.1.2.3. Study Report Body (report-body.pdf)
PK/PD Data Disk Submitted)	☒	☐			5.3.1.2.25. Individual Subject Data Listing (conc.xpt, pk.xpt)
Randomization Schedule	☒	☐			5.3.1.2.10. Randomisations Scheme (randomisation.pdf)
Protocol Deviations	☒	☐			5.3.1.2.17. Protocol Deviations (list-protocol-deviations.pdf)
Clinical Site	☒	☐			2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods (dbe-table-10.2.pdf)
Analytical Site	☐	☒			2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods (dbe-table-10.2.pdf)
Study Investigators	☒	☐			5.3.1.2.7. List Description Investigator Site (investigator-list.pdf)
Medical Records	☒	☐			5.3.1.2.24. Case Report Forms
Clinical Raw Data	☒	☐			5.3.1.2.24. Case Report Forms
Test Article Inventory	☒	☐			5.3.1.2.20. Compliance and Drug Concentration Data (list-comply-or-concentration.pdf)
BIO Batch Size	☒	☐			2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods (dbe-table-11.pdf)
Assay of Active Content Drug	☒	☐			2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods (dbe-table-11.pdf)
Content Uniformity	☒	☐			2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods (dbe-table-11.pdf)
Date of Manufacture	☒	☐			2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical

					Methods (dbe-table-11.pdf)
Exp. Date of RLD	☒	☐			2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods (dbe-table-11.pdf)
BioStudy Lot Numbers	☒	☐			2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods (dbe-table-11.pdf)
Statistics	☒	☐			5.3.1.2.12. Statistical Methods Interim Analysis Plan (statistical-methods.pdf)
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods (dbe-table-3.pdf) 5.3.1.2.3. Study Report Body (report-body.pdf)
Waiver requests for other strengths / supporting data	☒	☐			1.12.15 Request for Waiver of In Vivo Bioavailability Studies (biowaiver.pdf)

Additional comments regarding the ANDA:

- I. The test drug is Rivastigmine Transdermal System, 4.6 mg /24 hr and 9.5 mg /24 hr. The Reference Listed Drug (RLD) is EXELON[®] Patch (rivastigmine transdermal extended release film)¹, 9.5 mg/24 hr by Novartis (NDA# 022083, approved on July 6, 2007). EXELON[®] Patch is indicated for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's disease.
- II. As per Draft Guidance on Rivastigmine Transdermal System², the Office of Generic Drugs (OGD) recommends the following studies to establish bioequivalence to the RLD, EXELON[®] Patch:

Active ingredient: Rivastigmine
Form/Route: Film, Extended Release/Transdermal
Recommended studies: 2 studies

1. Type of study: Bioequivalence (BE) with Pharmacokinetic (PK) Endpoints and Adhesion
Study Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 9.5 mg/24 hr
Subjects: Healthy males and nonpregnant females, general population
Additional comments: The transdermal patch should be applied to clean, dry, hairless, intact healthy skin on the upper back, chest, or upper arm, as recommended in the approved reference listed drug (RLD) labeling and worn for 24 hours.

¹ Also known as Transdermal System (TDS)

² <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201278.pdf>

2. Type of study: Skin Irritation and Sensitization Study
Design: Randomized, evaluator-blinded, in vivo, within-subject repeat test
Strength: 4.6 mg/24 hr (Dose: One-half of 4.6 mg/24 hr patch)
Subjects: Healthy males and nonpregnant females, general population.
Additional comments: Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Rivastigmine in plasma (PK study only)

Bioequivalence based on (90% CI): Rivastigmine (PK study only)

Waiver request of in vivo testing: 4.6 mg/24 hr based on (i) acceptable bioequivalence studies on the 9.5 mg/24 hr strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity in the formulations across all strengths.

Dissolution test method and sampling times: Please note that a Dissolution Methods Database is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Development of an independent dissolution method is encouraged if the FDA recommended method is not suitable for the test product. In addition, dissolution testing using multi-pH media (pH 1.2, 4.5, and 6.8 buffer) should be conducted. Multipoint dissolution profiles should be obtained using a discriminating agitation speed. A surfactant may be used with appropriate justification. Specifications will be determined upon review of the data submitted in the application.

- III. Based on OGD's reviews for control correspondences #08-0180, 08-0526 and 10-0037, the first draft individual FDA guidance was published for Rivastigmine patch in February, 2010. The guidance recommended in 2/2010 required a PK study on 9.5 mg/24 hr and an adhesion study to be conducted along with irritation and sensitization studies using one entire patch of 4.6 mg/24 hr strength. However, in control correspondence #10-0371, Watson reported a significant number of adverse events (AEs), primarily application site AEs and gastrointestinal AEs during the conduct of the Rivastigmine Transdermal Irritation and Sensitization study using the full patch of 4.6 mg/24 hr. Based on clinical reviews for control correspondences #08-0189 and #10-0371, the previous draft Guidance was subsequently amended in June 2010 and the major changes were (1) to conduct the adhesion studies on the higher strength (9.5 mg/24 hr) along with the PK study and (2) to conduct the irritation and sensitization studies on one-half of 4.6 mg/24 hr patch.
- IV. The firm submitted the following studies in its original application dated 6/11/2012:
- PK and Adhesion Study #S10-1307** to assess the relative bioavailability and adhesion of Rivastigmine 9.5 mg / 24 hour Patch compared to that of Exelon 9.5 mg / 24 hour patch following a 24 hour application period in healthy adult subjects.
 - Irritation/Sensitization Study #C10-1870 (S11-0069, R10-1318)** on one half of 4.6 mg/24 hr patch to confirm that the test product is no more irritating and sensitizing than the reference product when applied over a continuous 21 day Induction Phase followed by a 48 hour Challenge Phase.
- V. The clinical reviewer reviewed firm's skin irritation/sensitization study C10-1087 (S11-0069, R10-1318) on one half of 4.6 mg/24 hr and the adhesion study from PK study (#S10-1307)

on 9.5 mg/24 hr), the data presented for comparison of skin irritation/sensitization and adhesion potential from these clinical BE studies were found acceptable for filing³.

- VI. Only the *in vivo* BE with PK endpoints study #R10-1307 was reviewed by the Division of Bioequivalence (DB) in the current checklist. PK study #R10-1307 is designed as a randomized, single-dose, two-way, open-label crossover bioavailability and adhesion study, comparing its test product, 9.5 mg/24 mL (batch #C0004AL0AU) to the RLD, EXELON[®] Patch, 9.5 mg/24 mL (lot # 1401B).

Composition of the test product

Component	Function	Amount in dried matrix / %	4.6 mg/24 hr Amount mg / 4.6 cm ²	9.5 mg/24 hr Amount mg / 9.2 cm ²	IIG Database Limit for Transdermal Products
Active layer, target area weight:	(b) (4)				
Rivastigmine	API	25	6.9 mg	13.8 mg	N/A

(b) (4)

Statistical Summary of *in vivo* BE study #R10-1307

Test Product A vs. Reference Product B Least Squares Means, Geometric Means, Ratios of Means, and 90% CIs Ln-Transformed Data Rivastigmine N = 27						
Parameter	Least Squares Means		Geometric Means*		% Ratio	90% CI (Lower Limit, Upper Limit)
	Test Product A: Rivastigmine Transdermal System, 9.5 mg/24 hours	Reference Product B: Exelon Patch, 9.5 mg/24 hours	Test Product A: Rivastigmine Transdermal System, 9.5 mg/24 hours	Reference Product B: Exelon Patch, 9.5 mg/24 hours		
AUC _{0-t} (pg-hr/mL)	12.004	11.877	163464.95	143876.95	113.61	(106.60, 121.09)
AUC _{0-inf} (pg-hr/mL)	12.010	11.883	164334.80	144824.77	113.47	(106.50, 120.90)
C _{max} (pg/mL)	9.112	8.971	9067.37	7869.17	115.23	(107.05, 124.02)

*Geometric means are based on the exponential of LSM of ln-transformed values.

The confidence intervals for PK parameters (AUC_t, AUC_i and C_{max}) meet the BE acceptable

³ DARRTS: REV-CLINICAL-06(Filing Review) for ANDA 204403, final date 7/18/2012.

criteria of 80-125%.

- VII. *In vitro* comparative dissolution testing has been performed on Alvogen' Rivastigmine Transdermal System and Exelon® Patch (rivastigmine transdermal system), 4.6 mg/24 hr and 9.5 mg/24 hr strengths. Comparison testing was conducted in (b) (4) of 0.9% NaCl and three pH media (pH1.2, 4.5, and 6.8 buffer) using (b) (4). The dissolution testing was also conducted in 500 ml of 0.9% NaCl and multi-pH media (pH1.2, 4.5, and 6.8 buffer) using modified USP Apparatus 6 (rotating cylinder) at 50 rpm.
- VIII. In this application (module 1.12.15), the firm has requested a waiver of *in vivo* testing for lower strength, 4.6 mg/24 hr based on (1) PK and adhesion study #R10-1307 on 9.5 mg/24 hr and skin irritation/sensitization study # C10-1087(S11-0069, R10-1318) on half size of 4.6 mg/24 hr, (2) *in vitro* dissolution testing and (3) formulation proportionality.

From a bioequivalence standpoint this application is acceptable for filing.

OUTCOME PAGE

Completed Assignment for 204403 ID: 17592

Reviewer: Xia, Li

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Rivastigmine Transdermal System, 4.6 mg/24 hr and 9.5 mg/24 hr

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
17592	6/11/2012	Filing Checklist (REGULAR)	ANDA Filing Checklist	1	1
				Total:	1

DBE2 Productivity points:

Checklist	
First Generic Checklist	1
<i>Total</i>	<i>1</i>

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LI XIA
08/16/2012

XIAOJIAN JIANG
08/17/2012

ETHAN M STIER on behalf of BARBARA M DAVIT
08/17/2012

**DIVISION OF CLINICAL REVIEW CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS**

ANDA# 204403 FIRM NAME Alvogen Pine Brook, Inc.

DRUG NAME Rivastigmine Transdermal System, 4.6 mg per 24 hours and 9.5 mg per 24 hours

DOSAGE FORM Transdermal Patch

REFERENCE LISTED DRUG (RLD) Exelon Patch (NDA 022083) 9.5 mg per 24 hours

Requested by: Howard, Eda Date: 6/25/12
Regulatory Support Team, (HFD-615)

Summary of Findings by Division of Clinical Review	
X	Study meets statutory requirements The Division of Clinical Review (DCR) does not require skin irritation/sensitization/adhesion studies for lower strength product (4.6 mg/24 hours). Therefore, the filing review decision regarding the waiver request of the BE study requirement for that strength product is deferred to the DB II. Please see comments to be conveyed to the sponsor.
	Study does NOT meet statutory requirements Reason:
	Waiver meets statutory requirements
	Waiver does NOT meet statutory requirements Reason:

RECOMMENDATION: X COMPLETE INCOMPLETE

Reviewed by:

Reviewer
Carol Y. Kim, Pharm.D.
Clinical Reviewer

Date: _____

John R. Peters, M.D.
Director, Division of Clinical Review

Date: _____

Item Verified:	Irritation/ Sensitization #C10-1870; 4.6 mg/24hr		Comments
	YES	NO	
Protocol	X		Both ½ size of 4.6 mg/24 hr of the test and reference products were applied on each subject.
Summary of Study	X		
Clinical Site (s)	X		
Study Investigator (s)	X		
List of subjects included in PP/ (M)ITT populations per treatments	X		
List of subjects excluded/ from PP/ (M)ITT per treatments	X		
Reasons for discontinuation from the study if discontinued	X		
Adverse Events	X		
Concomitant Medications	X		
Individual subject's scores/data per visit	X		
Pre-screening of Patients	X		
IRB Approval	X		
Consent Forms	X		
Randomization Schedule	X		
Protocol Deviations	X		
Case Report Forms	X		Electronic case report forms (eCRFs) used. Need source documents for irritation/sensitization scores because they were not collected in the eCRFs.
Primary data in SAS .xpt file	X		
Financial Disclosure	X		
Study Results	X		

Clinical Raw Data/ Medical Records		X	Only electronic case report forms provided.
Composition	X		
BioStudy Lot Numbers	X		
Date of Manufacture	X		
Exp. Date of RLD	X		
Statistical Reports	X		
Defined BE endpoints		X	N/A
Summary results provided by the firm indicate no worse skin irritation, adhesion, and sensitization properties of the test product compared to that of the RLD	X		See comments below
Waiver requests for other strengths / supporting data	X		Lower strength of Rivastigmine Transdermal System, 4.6 mg/24 hours

Comments NOT to be conveyed to the sponsor

The sponsor conducted a skin irritation/sensitization study (C10-1870) using ½ size of 4.6 mg/24 hours of the test and reference products on each subject. Adhesion performance of the test product and the reference listed drug (9.5 mg/24 hours) was evaluated in a pharmacokinetic study (R10-1307).

In a skin irritation/sensitization study (C10-1870), one-half (1/2) of the test and one-half (1/2) of the reference product were applied to separate sites on the upper arms worn for 24 hours during the 21 days of induction phase. After 14 days of rest period, one-half (1/2) of the test and one-half (1/2) of the reference product were applied on the upper back and removed 48 +/-4 hours after application. Skin reactions indicative of sensitization were evaluated at 30 minutes, 24, 48, and 72 hours after patch removal. Hypoallergenic tape was used to ensure the continuous attachment of the patches to the skin.

1. The data presented for comparison of skin irritation potential are acceptable for review.

The OGD Draft Guidance recommends use of ½ size of 4.6 mg/24 hours of the test and reference products for evaluation of skin irritation and sensitization potentials of Rivastigmine Transdermal System, 9.6 mg/24 hours.

A. The sponsor’s summary of skin irritation analysis (study C10-1870) is shown below.

Table 11.4.1 Statistical Results of Induction Phase Irritation Analysis (PPPI Population) (N=262)

Variable	Hypotheses	A-1.25B	Upper Bound of One-Sided 95% Confidence Limit
Cumulative Irritation Scores (Dermal Response + Other Effect Scores) (Test - 1.25*Reference)	H ₀ : $\mu_T - 1.25 \mu_R > 0$ H ₁ : $\mu_T - 1.25 \mu_R \leq 0$	-8.60592	-7.82006

* A = Test Product, B = Reference Product

Table 11.4.2 Summary of Descriptive Statistics for Cumulative Combined Irritation Scores for Test Product and Reference Product Using LOCF

Cumulative Irritation Scores (Dermal Response + Other Effects)	Test Product: Rivastigmine Transdermal System, 4.6 mg/24 hours	Reference Product: Exelon Patch (Rivastigmine Transdermal System) 4.6 mg/24 hours
N	262	262
Mean	32.02	32.50
Median	34	35
Standard Deviation	18.57	17.64
Max	121	121
Min	2	2

Table 11.4.3 Summary of Induction Phase Irritation Scores and Frequencies using LOCF for Test Product A from Day 2 to Day 12 (PPPI - N=262)

Score	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)	Day 8 N (%)	Day 9 N (%)	Day 10 N (%)	Day 11 N (%)	Day 12 N (%)
0	155 (59.16%)	117 (44.66%)	104 (39.69%)	92 (35.11%)	75 (28.63%)	67 (25.57%)	59 (22.52%)	48 (18.32%)	37 (14.12%)	30 (11.45%)	30 (11.45%)
1	97 (37.02%)	129 (49.24%)	128 (48.85%)	129 (49.24%)	127 (48.47%)	112 (42.75%)	116 (44.27%)	90 (34.35%)	96 (36.64%)	96 (36.64%)	91 (34.73%)
2	10 (3.82%)	12 (4.58%)	22 (8.40%)	29 (11.07%)	48 (18.32%)	69 (26.34%)	72 (27.48%)	108 (41.22%)	113 (43.13%)	120 (45.80%)	119 (45.42%)
3	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.76%)	2 (0.76%)	3 (1.15%)	3 (1.15%)	4 (1.53%)	4 (1.53%)	4 (1.53%)	4 (1.53%)
4	0 (0.00%)	3 (1.15%)	6 (2.29%)	8 (3.05%)	8 (3.05%)	9 (3.44%)	9 (3.44%)	9 (3.44%)	9 (3.44%)	9 (3.44%)	14 (5.34%)
5	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.38%)	1 (0.38%)	1 (0.38%)	1 (0.38%)	1 (0.38%)
6	0 (0.00%)	1 (0.38%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	3 (1.15%)

Note: Results are based on the scores of original sites.

Table 11.4.4 Summary of Induction Phase Irritation Scores and Frequencies using LOCF for Test Product A from Day 13 to Day 22 (PPPI - N=262)

Score	Day 13 N (%)	Day 14 N (%)	Day 15 N (%)	Day 16 N (%)	Day 17 N (%)	Day 18 N (%)	Day 19 N (%)	Day 20 N (%)	Day 21 N (%)	Day 22 N (%)
0	17 (6.49%)	30 (11.45%)	16 (6.11%)	14 (5.34%)	6 (2.29%)	13 (4.96%)	8 (3.05%)	5 (1.91%)	5 (1.91%)	6 (2.29%)
1	84 (32.06%)	75 (28.63%)	85 (32.44%)	81 (30.92%)	83 (31.68%)	77 (29.39%)	77 (29.39%)	78 (29.77%)	75 (28.63%)	75 (28.63%)
2	132 (50.38%)	124 (47.33%)	125 (47.71%)	125 (47.71%)	127 (48.47%)	122 (46.56%)	124 (47.33%)	123 (46.95%)	124 (47.33%)	119 (45.42%)
3	5 (1.91%)	5 (1.91%)	6 (2.29%)	7 (2.67%)	8 (3.05%)	12 (4.58%)	12 (4.58%)	14 (5.34%)	14 (5.34%)	18 (6.87%)
4	17 (6.49%)	21 (8.02%)	21 (8.02%)	24 (9.16%)	26 (9.92%)	26 (9.92%)	29 (11.07%)	30 (11.45%)	32 (12.21%)	32 (12.21%)
5	4 (1.53%)	4 (1.53%)	6 (2.29%)	8 (3.05%)	9 (3.44%)	9 (3.44%)	9 (3.44%)	9 (3.44%)	9 (3.44%)	9 (3.44%)
6	3 (1.15%)	3 (1.15%)	3 (1.15%)	3 (1.15%)	3 (1.15%)	3 (1.15%)	3 (1.15%)	3 (1.15%)	3 (1.15%)	3 (1.15%)

Note: Results are based on the scores of original sites.

Table 11.4.5 Summary of Induction Phase Irritation Scores and Frequencies using LOCF for Reference Product B from Day 2 to Day 12 (PPPI - N=262)

Score	Day 2 N (%)	Day 3 N (%)	Day 4 N (%)	Day 5 N (%)	Day 6 N (%)	Day 7 N (%)	Day 8 N (%)	Day 9 N (%)	Day 10 N (%)	Day 11 N (%)	Day 12 N (%)
0	147 (56.11%)	113 (43.13%)	104 (39.69%)	88 (33.59%)	64 (24.43%)	51 (19.47%)	43 (16.41%)	35 (13.36%)	24 (9.16%)	18 (6.87%)	15 (5.73%)
1	102 (38.93%)	125 (47.71%)	123 (46.95%)	124 (47.33%)	125 (47.71%)	111 (42.37%)	113 (43.13%)	99 (37.79%)	105 (40.08%)	104 (39.69%)	103 (39.31%)
2	13 (4.96%)	19 (7.25%)	24 (9.16%)	38 (14.50%)	61 (23.28%)	87 (33.21%)	93 (35.50%)	115 (43.89%)	119 (45.42%)	126 (48.09%)	125 (47.71%)
3	0 (0.00%)	0 (0.00%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	4 (1.53%)
4	0 (0.00%)	3 (1.15%)	7 (2.67%)	8 (3.05%)	8 (3.05%)	8 (3.05%)	8 (3.05%)	8 (3.05%)	9 (3.44%)	9 (3.44%)	11 (4.20%)
5	0 (0.00%)	1 (0.38%)	1 (0.38%)	1 (0.38%)	1 (0.38%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)
6	0 (0.00%)	1 (0.38%)	1 (0.38%)	1 (0.38%)	1 (0.38%)	1 (0.38%)	1 (0.38%)	1 (0.38%)	1 (0.38%)	1 (0.38%)	2 (0.76%)

Note: Results are based on the scores of original sites.

Table 11.4.6 Summary of Induction Phase Irritation Scores and Frequencies using LOCF for Reference Product B from Day 13 to Day 22 (PPPI – N=262)

Score	Day 13 N (%)	Day 14 N (%)	Day 15 N (%)	Day 16 N (%)	Day 17 N (%)	Day 18 N (%)	Day 19 N (%)	Day 20 N (%)	Day 21 N (%)	Day 22 N (%)
0	5 (1.91%)	12 (4.58%)	15 (5.73%)	8 (3.05%)	10 (3.82%)	9 (3.44%)	3 (1.15%)	6 (2.29%)	3 (1.15%)	6 (2.29%)
1	88 (33.59%)	93 (35.50%)	80 (30.53%)	87 (33.21%)	82 (31.30%)	84 (32.06%)	84 (32.06%)	79 (30.15%)	76 (29.01%)	76 (29.01%)
2	142 (54.20%)	129 (49.24%)	135 (51.53%)	130 (49.62%)	130 (49.62%)	126 (48.09%)	125 (47.71%)	127 (48.47%)	130 (49.62%)	124 (47.33%)
3	6 (2.29%)	6 (2.29%)	7 (2.67%)	7 (2.67%)	7 (2.67%)	8 (3.05%)	9 (3.44%)	9 (3.44%)	9 (3.44%)	12 (4.58%)
4	15 (5.73%)	16 (6.11%)	17 (6.49%)	20 (7.63%)	23 (8.78%)	25 (9.54%)	31 (11.83%)	31 (11.83%)	34 (12.98%)	34 (12.98%)
5	4 (1.53%)	4 (1.53%)	6 (2.29%)	8 (3.05%)	8 (3.05%)	8 (3.05%)	8 (3.05%)	8 (3.05%)	8 (3.05%)	8 (3.05%)
6	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)	2 (0.76%)

Note: Results are based on the scores of original sites.

2. The data presented for comparison of skin sensitization potential are acceptable for review.

According to the sponsor, 43 subjects (43/228 or 18.9%) demonstrated evidence of a potential sensitization reaction to both test and reference products. No subject demonstrated a potential sensitization reaction to only the test or the reference product.

The sponsor's summary for the Challenge Phase is shown below.

Table 11.4.9 Statistical Results of Challenge Phase Irritation Analysis (PPPS Population) (N=228)

Variable	Hypotheses	A-1.25B	Upper Bound of One-Sided 95% Confidence Limit
Cumulative Irritation Scores (Dermal Response + Other Effect Scores) (Test – 1.25*Reference)	$H_0: \mu_T - 1.25 \mu_R > 0$ $H_1: \mu_T - 1.25 \mu_R \leq 0$	-0.85239	-0.73758

* A = Test Product, B = Reference Product

Table 11.4.10 Summary of Challenge Phase Irritation Evaluation Scores and Frequencies for Test Product A During the Challenge Phase (PPPS – N=229)

Combined Irritation Score	Time Point After Dose-Removal			
	30 minute N (%)	24 hour N (%)	48 hour N (%)	72 hour N (%)
0	58 (25.33%)	82 (35.81%)	114 (49.78%)	169 (73.80%)
1	69 (30.13%)	86 (37.55%)	75 (32.75%)	30 (13.10%)
2	100 (43.67%)	59 (25.76%)	37 (16.16%)	24 (10.48%)
3	2 (0.87%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
4	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (1.31%)
5	0 (0.00%)	2 (0.87%)	3 (1.31%)	3 (1.31%)

Table 11.4.11 Summary of Challenge Phase Irritation Evaluation Scores and Frequencies for Reference Product During the Challenge Phase (PPPS – N=228)

Combined Irritation Score	Time Point After Dose-Removal			
	30 minute N (%)	24 hour N (%)	48 hour N (%)	72 hour N (%)
0	52 (22.81%)	81 (35.53%)	111 (48.68%)	171 (75.00%)
1	72 (31.58%)	88 (38.60%)	77 (33.77%)	27 (11.84%)
2	102 (44.74%)	58 (25.44%)	36 (15.79%)	24 (10.53%)
3	2 (0.88%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
4	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (1.32%)
5	0 (0.00%)	1 (0.44%)	4 (1.75%)	3 (1.32%)

Table 11.4.12 Descriptive Statistics of Combined Irritation Scores for Test Product During the Challenge Phase (PPPS – N=229)

Descriptive Statistics	30 min	24 hour	48 hour	72 hour
N	229	229	229	229
Mean	1.20	0.93	0.72	0.46
Standard Deviation	0.83	0.87	0.89	0.94
Median	1	1	1	0
Min	0	0	0	0
Max	3	5	5	5

Table 11.4.13 Descriptive Statistics of Combined Irritation Scores for Reference Product During the Challenge Phase (PPPS – N=228)

Descriptive Statistics	30 min	24 hour	48 hour	72 hour
N	228	228	228	228
Mean	1.24	0.92	0.74	0.45
Standard Deviation	0.81	0.82	0.93	0.94
Median	1	1	1	0
Min	0	0	0	0
Max	3	5	5	5

3. The data presented for comparison of skin adhesion performance (i.e., 9.5 mg/24 hours) are acceptable for review.

In a single application, two-period, crossover pharmacokinetic study (R10-1307), adhesion performance of 9.5 mg/24 hours of test product or the reference listed drug was evaluated at 0 (immediately after application), 2, 4, 6, 8, 10, 12, 18, and 24 hours post application. Taping or any external reinforcement of the patch was not allowed. According to the sponsor's analysis of cumulative adhesion score, the upper bound of the one-sided 95% CI for the mean difference between test and 1.25 X reference was 0. Based on frequency of adhesion scores, the test product's adhesion performance does not appear to be any worse than that of the RLD. No subject had a score of 3 or 4.

The sponsor's summary of adhesion analysis is shown below.

Table 11.4.2 Summary of Cumulative Adhesion Score – PPPA

	Test Product A: Rivastigmine Transdermal System, 9.5 mg/24 hours	Reference Product B: Exelon Patch, 9.5 mg/24 hours
N	27	27
Arithmetic Mean	0.70	0.52
Standard Deviation	1.49	1.05
Median	0.00	0.00
Max	0.00	0.00
Min	6.00	4.00

Table 11.4.4 Summary of 95% Bootstrapping Confidence Limit -- CAS (PPPA – N=27)

Variable	Median Difference	Upper Bound of 95% Bootstrap Confidence Limit of the Median Difference
Cumulative Adhesion Scores (Test – 1.25*Reference)	0.00	0.00

Table 11.4.3 Frequency of Adhesion Scores – PPPA

Treatment	Score	Hour 0	Hour 2	Hour 4	Hour 6	Hour 8	Hour 10	Hour 12	Hour 18	Hour 24
A	0	27 (100.00%)	27 (100.00%)	27 (100.00%)	27 (100.00%)	25 (92.59%)	24 (88.89%)	23 (85.19%)	21 (77.78%)	24 (88.89%)
	1	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (7.41%)	3 (11.11%)	4 (14.81%)	6 (22.22%)	2 (7.41%)
	2	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)
	3	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	4	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
B	0	27 (100.00%)	27 (100.00%)	27 (100.00%)	27 (100.00%)	26 (96.30%)	24 (88.89%)	26 (96.30%)	22 (81.48%)	23 (85.19%)
	1	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.70%)	3 (11.11%)	1 (3.70%)	5 (18.52%)	4 (14.81%)
	2	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	3	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	4	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Reviewer’s Comment: No subject had an adhesion score greater than 2. Of 27 subjects, one subject with the test product and no subject with the reference product had a score of 2.

From the Division of Clinical Review (DCR)’s perspective, no skin irritation/sensitization/adhesion study is requested for lower strength product (4.6 mg/24 hours). Therefore, the filing review decision for the waiver request of the BE study requirement is deferred to the DB II.

The composition of the test product is shown below.

Alvogen Pine Brook, Inc.
 ANDA #204403 (Pre-Assigned)
 Rivastigmine Transdermal System, 4.6 mg/24hr and 9.5 mg/24hr

m3/3.2.P
DRUG PRODUCT

Component	Function	Amount in dried matrix / %	4.6 mg/24 hr Amount mg / 4.6 cm ²	9.5 mg/24 hr Amount mg / 9.2 cm ²	IIG Database Limit for Transdermal Products
Active layer, target area weight: (b) (4)					
Rivastigmine	API	25	6.9 mg	13.8 mg	N/A
(b) (4)					

Comments to be conveyed to the sponsor

The data submitted to your application are acceptable for receiving your ANDA. Please note that the acceptability of your data and analyses will be evaluated during the review of the application.

Please include the following additional information for the review:

1. Source documents for each irritation/sensitization score per visit could not be located in case report forms for study C10-1870.
2. The “define.pdf” is incomplete because it did not include detailed description for each code used. As recommended in the OGD Draft Guidance for this product, a detailed description of the codes that are used for each variable in each of the SAS datasets should be included. For example, in a dataset “ds001.xpt”, the code of “L” in variable “F_status” should be defined.
3. “Summary.xpt” dataset has missing information (i.e., it is blank) under variables, “PPIRR”, “PPIRR_RS”, “PPSEN”, and “PPSEN_RS”. For “PPIRR” and “PPSEN”, either “yes” or “no” should be defined for each subject to indicate whether they were included or excluded from the irritation or sensitization analysis. For “PPIRR_RS” and “PPSEN_RS”, reason for exclusion should be defined for each subject.
4. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NOLOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set) for skin irritation/sensitization study. For each subject, include variables to indicate (e.g., yes or no) whether they were included or excluded from the irritation or sensitization analyses.
5. A dataset for eligibility exception (i.e., “ie001”) is blank. Provide complete data.
6. The response (e.g., yes or no) for each inclusion/exclusion criterion for each subject should be provided in SAS .xpt dataset. For example, please see below table for details.

Subject number	Inclusion criterion #1	Inclusion criterion #2	Inclusion criterion #3	
	Yes	Yes	yes	

7. Frequency tables for the following: 1) number of subjects with patch moved and 2) the number of patches moved due to excessive irritation for each treatment group.

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/s/

CAROL Y KIM
07/18/2012

JOHN R PETERS
07/18/2012

MEMORANDUM

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

DATE : June 20, 2012

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Rivastigmine Transdermal System Extended-release Film, 4.6 mg/24 hr and 9.5 mg/24 hr (Patch) to determine if the application is substantially complete for filing.

Alvogen Pine Brook, Inc. has submitted ANDA 204403 for Rivastigmine Transdermal System Extended-release Film, 4.6 mg/24 hr and 9.5 mg/24 hr (Patch). In order to accept an ANDA, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Alvogen Pine Brook, Inc. on June 12, 2012 for its Rivastigmine Transdermal System product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

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/s/

EDA E HOWARD
06/25/2012