CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 78830

Name: Scopolamine Transdermal Therapeutic System, 1 mg/3 days

Sponsor: Perrigo Pharmaceutical Company

Approval Date: January 30, 2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78830

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78830

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 078830

ANDA APPROVAL

Perrigo R&D Company
Attention: Shilpa Patel
Senior Manager - Regulatory Affairs
515 Eastern Avenue
Allegan, Michigan 49010

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated February 23, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Scopolamine Transdermal Therapeutic System, 1 mg/3 days.

Reference is also made to the Complete Response letter issued by this office on May 31, 2013, and to your amendments dated March 14, August 19, and December 4, 2014.

This letter is intended to correct the Approval Letter issued on January 30, 2015, which displayed the incorrect ANDA number, (b) (4). The correction has been made and the ANDA number has been changed to 078830. The effective approval date will remain January 30, 2015, the date of the original approval letter.

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 the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Scopolamine Transdermal Therapeutic System, 1 mg/3 days to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug product (RLD), Transderm Scop, 1 mg/3 days, of Novartis Pharmaceuticals Corporation.

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

The dissolution testing should be conducted using the FDA-recommended method of 25 x 150 mm test tubes containing 20 mL of distilled water at 32°C ± 0.3°C using USP Apparatus 7 (reciprocating disk) at a stroke of 2-3 cm at a rate of 30-60 cycles/minute. The test product should meet the following specifications:

6 hr: (b) (4) %
24 hr: (b) (4) %
48 hr: (b) (4) %

72 hr: (b) (4) %

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 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 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

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: 2015.02.02 14:31:35 -05'00'

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78830

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 078830

COMPLETE RESPONSE

To: Perrigo R&D Company
ATTN: James Chambers,
Senior Managers - Regulatory Affairs
515 Eastern Avenue
Allegan, Michigan 49010

Dear Sir,

Please refer to your Abbreviated New Drug Application (ANDA) dated February 23, 2007 and received on February 26, 2007, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Scopolamine Transdermal Therapeutic System, 1 mg/3 days.

We acknowledge receipt of your amendments dated September 20, 2007; January 4, and December 11, 2008; April 17, May 22, and August 13, 2012; March 19, 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. The deficiencies presented below represent **MINOR** deficiencies.

1. (b) (4)

2. The Agency requires evidence that the formulation of a generic product is not less safe than the RLD. We acknowledge that it is possible that different transdermal formulations of the same drug may have different responses to "in-use conditions". To ensure that the RLD labeling with respect to swimming/showering is applicable to the ANDA product, please provide information about the formulation performance to ensure that the sensitivity to in-use conditions like water/hot water exposure of the generic product is not more pronounced than that of the RLD. You may design and provide an in vitro study (e.g., skin flux permeation study with "stressed" conditions to mimic certain in-use conditions) to compare in vitro release data to the RLD at normal and "stress" situations: If the generic product was not more sensitive than the RLD, it would be acceptable. Such in vitro data would assure that the proposed generic TDDS product would not create a greater risk when exposed to in-use conditions than the RLD. Please refer to the FDA response to the CP 2012-P-0932 (see link below) for additional information.

http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0932-0003

3 [redacted]

CLINICAL

The Division of Clinical Review has completed its review and the following deficiencies have been identified:

1. You have not provided adequate data to ensure that the adhesive performance of your product is at least as good as that of the RLD.

   In the pharmacokinetic/adhesion study (PRG-604), your product was statistically significantly less adhesive than the reference product. The study failed to show non-inferiority of your Scopolamine Extended-release Transdermal Film to the reference product with regard to adhesion performance.

2. For future bioequivalence studies (including test-reference comparisons of skin irritation, sensitization, and adhesion), the final study report must include a discussion of the retention of testing samples. Please refer to 21 CFR 320.38 and 320.63 regarding retention of study drug samples. For more information, please refer to the Guidance for Industry: "Handling and Retention of BA and BE Testing Samples" (May 2004). Retention samples must be randomly selected from each drug shipment by each study site and retained by the investigator or an independent third party not involved with packaging and labeling of the study products. Retention samples are not to be returned to the sponsor at any time. If these recommendations are not followed for future bioequivalence studies, then the study may be found unacceptable to support product approval. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, "Good Clinical Practice: Consolidated Guideline."

BIOEQUIVALENCE

The Division of Bioequivalence has completed its review and has no further questions at this time.

We concur with your dissolution testing method and specifications as follows:

The dissolution testing should be conducted using the FDA-recommended method of 25 x 150 mm test tubes containing 20 mL of distilled water at 32ºC ± 0.3ºC using USP Apparatus 7 (reciprocating disk) at a stroke of 2-3 cm at a rate of 30-60 cycles/minute. The test product should meet the following specifications:

6 hr: [redacted]%
24 hr: [redacted]%
48 hr: [redacted]%
72 hr: [redacted]%

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.

LABELING

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated May 22, 2012.

Please continue to monitor available labeling resources such as 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

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle. The resubmission to this will be considered to represent a MINOR AMENDMENT. The designation as a **RESUBMISSION/AFTER ACTION – MINOR COMPLETE RESPONSE AMENDMENT** should appear prominently in your cover letter. In addition, please designate in bold on your cover letter each review discipline (Product Quality (CMC), Labeling, Bioequivalence) you are providing responses to.

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 dose 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 Linda Park, Regulatory Project Manager, at (240) 276-8536.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
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/

ROBERT L WEST

05/31/2013

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78830

LABELING

Final Printed Labeling
Carton - 4 ct

12-02-14

Final Printed Labeling
Carton - 10 ct

EFH 1374

NDC 45802-**580**-46

Scopolamine
Transdermal System
1 mg/3 days

10 Patches

Scopolamine
Transdermal System
1 mg/3 days

Each patch contains 1.3 mg scopolamine formulated to deliver *in vivo* approximately 1 mg over 3 days. The inactive components are crospovidone, isopropyl palmitate, light mineral oil, polyisobutylene, ethylene vinyl acetate copolymer and aluminized polyester film.

Dosage and Administration:

1. Before applying patch, wash and dry hands thoroughly.
2. **Use only one patch at a time. Do not cut the patch.**
3. Remove and discard the clear plastic backing from the patch.
4. Apply to the hairless area behind one ear as indicated in accompanying prescribing information.
5. Wash and dry hands thoroughly after application.

See accompanying prescribing information for details.

CONTENTS - 10 PATCHES

Caution: May cause drowsiness, blurred vision. To avoid possible burns, remove the scopolamine transdermal system before undergoing an MRI (Magnetic Resonance Imaging) procedure.

Keep this and all medication out of reach of children.

Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature].

FOIL-SEALED FOR YOUR PROTECTION. DO NOT USE IF SEAL IS BROKEN.

Mfd. by:
AVEVA Drug Delivery Systems
An APOTEX Company
Miramar, FL 33025

Distributed By
Perrigo®
Allegan, MI 49010
www.perrigo.com

: 5A846 RC C5 Rev 11-14

Rx Only

NDC 45802-**580**-46

Scopolamine
Transdermal System
1 mg/3 days

10 Patches

NDC 45802-**580**-46

Scopolamine
Transdermal System
1 mg/3 days

Formulated delivery of approximately 1 mg over three days

Motion Sickness and Post-operative Nausea & Vomiting Prevention Patches

10 Patches

Perrigo®

N 3 45802-580-46 7

12-02-14

Final Printed Labeling
Carton - 24 ct

EFH 1374

NDC 45802-**580**-62

Scopolamine
Transdermal System
1 mg/3 days

24 Patches

Scopolamine
Transdermal System
1 mg/3 days

Each patch contains 1.3 mg scopolamine formulated to deliver *in vivo* approximately 1 mg over 3 days. The inactive components are crospovidone, isopropyl palmitate, light mineral oil, polyisobutylene, ethylene vinyl acetate copolymer and aluminized polyester film.

Dosage and Administration:

1. Before applying patch, wash and dry hands thoroughly.
2. **Use only one patch at a time. Do not cut the patch.**
3. Remove and discard the clear plastic backing from the patch.
4. Apply to the hairless area behind one ear as indicated in accompanying prescribing information.
5. Wash and dry hands thoroughly after application.

See accompanying prescribing information for details.

CONTENTS - 24 PATCHES

Caution: May cause drowsiness, blurred vision. To avoid possible burns, remove the scopolamine transdermal system before undergoing an MRI (Magnetic Resonance Imaging) procedure.

Keep this and all medication out of reach of children.

Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature].

FOIL-SEALED FOR YOUR PROTECTION. DO NOT USE IF SEAL IS BROKEN.

Mfd. by:
AVEVA Drug Delivery Systems
An APOTEX Company
Miramar, FL 33025

Distributed By
Perrigo®
Allegan, MI 49010
www.perrigo.com

: 5A8&2 RC CS Rev 11-14

NDC 45802-**580**-62

Scopolamine
Transdermal System
1 mg/3 days

24 Patches

Rx Only

NDC 45802-**580**-62

Scopolamine
Transdermal System
1 mg/3 days

Formulated delivery of approximately 1 mg over three days

Motion Sickness and Post-operative Nausea & Vomiting Prevention Patches

24 Patches

Perrigo®

N 3 45802-580-62 7

12-02-14

Final Printed Labeling
Patch

FPC 247

FRONT

BACK

12-02-14

Page 1

FLAT SIZE = 11.875" x 11.875" FOLD SIZE = 3.0" x 2.0"

GLUE PANEL
NO COPY

GLUE PANEL
NO COPY

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Rev 11-14

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PAR 11-14

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use scopolamine transdermal system safely and effectively. See full prescribing information for scopolamine transdermal system.

Scopolamine Transdermal System 1 mg/3 days
Initial U.S. Approval: 1979

----------INDICATIONS AND USAGE----------

Scopolamine transdermal system is an anticholinergic agent indicated in adults for the prevention of nausea and vomiting associated with:

- Motion Sickness (1.1)
- Post Operative Nausea and Vomiting (PONV) (1.2)

----------DOSAGE AND ADMINISTRATION----------

DO NOT cut the patch. Apply ONE patch in the postauricular area to prevent:

Motion Sickness	• Apply 4 hrs before antiemetic effect is required- for use up to 3 days (2.1) • For use longer than 3 days, remove current patch and place new patch behind other ear (2.2)
Post Operative Nausea and Vomiting (PONV)	• Apply evening before scheduled surgery (2.1) • For cesarean section, apply 1 hour prior to surgery (2.1) • Discard 24 hrs after surgery (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Continuous release, circular, flat, tan colored patch (1.3 mg scopolamine) (3)

----------CONTRAINDICATIONS----------

- Patients with angle closure glaucoma (4, 6.2)
- Persons who are hypersensitive to scopolamine or to other belladonna alkaloids (4, 7)

----------WARNINGS AND PRECAUTIONS----------

- Use with caution in patients with open angle glaucoma (5.1)
- Stop use if patient experiences symptoms of angle closure glaucoma (5.1, 6.2)
- Can cause temporary dilation and blurred vision if scopolamine contacts the eyes (5.2, 6, 16)
- Use caution in patients with a history of seizures or psychosis (5.4)
- Use with caution in patients with pyloric obstruction, urinary bladder neck obstruction, or patients suspected of having intestinal obstruction (5.3)
- Stop use if patient has difficulty urinating (5.3, 6)
- Idiosyncratic reactions, such as confusion, agitation, speech disorder, hallucinations, paranoia and delusions, may occur with therapeutic doses of scopolamine (5.5, 6.2)
- A safe and effective dose has not been established in the pediatric population (5.6, 8.4)
- Use with caution in the elderly because of the increased likelihood of CNS effects, such as hallucinations, confusion and dizziness (5.6, 8.5)
- Should be used with caution in patients with impaired renal or hepatic function because of the increased likelihood of CNS effects (5.6, 8.5, 8.6)
- May cause drowsiness or disorienting effects, therefore patients should be cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery (5.7)
- Skin burns have been reported in patients undergoing MRI testing (5.8)

----------ADVERSE REACTIONS----------

Most common adverse reactions during motion sickness clinical trials are dry mouth, drowsiness and blurred vision. (6.1)
Most common adverse reactions during PONV trials (≥ than 3%) are dry mouth, dizziness, somnolence, urinary retention, agitation, visual impairment, confusion, mydriasis and pharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Perrigo at 1-866-634-9120 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Absorption of oral medications may be decreased (7)
- Use with care while taking sedatives, tranquilizers or alcohol (7)
- Potential interactions with drugs having anticholinergic properties (7)
- Scopolamine interferes with the gastric secretion test (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Nursing mothers: Caution should be exercised when administered to a nursing woman (8.3)

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

Revised: November 2014

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Motion Sickness
1.2 Post Operative Nausea and Vomiting (PONV)
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17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Motion Sickness

Scopolamine transdermal system is indicated in adults for prevention of nausea and vomiting associated with motion sickness. *[see Clinical Studies (14.1)]*

1.2 Post Operative Nausea and Vomiting (PONV)

Scopolamine transdermal system is indicated in adults for prevention of nausea and vomiting associated with recovery from anesthesia and/or opiate analgesia and surgery. *[see Clinical Studies (14.2)]*

2 DOSAGE AND ADMINISTRATION

Each scopolamine transdermal system is formulated to deliver *in-vivo* approximately 1 mg of scopolamine over 3 days. Only one patch should be worn at any time. **Do not cut the patch.**

The patch should be applied only to the skin in the postauricular (hairless area behind one ear) area.

Handling

After the patch is applied on the dry skin healed, the hands should be washed thoroughly with soap and water and dried. Upon removal, the patch should be discarded. To prevent any traces of scopolamine from coming into direct contact with the eyes, after administration of the patch, the hands and the application site should be washed thoroughly with soap and water and dried. *[see How Supplied/Storage and Handling (16) and Patient Counseling Information (17)]*

2.1 Initiation of Therapy

Motion Sickness

- To prevent the nausea and vomiting associated with motion sickness, one scopolamine transdermal system (formulated to deliver approximately 1 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required.

Post Operative Nausea and Vomiting

- To prevent post operative nausea and vomiting, one scopolamine transdermal system should be applied the evening before scheduled surgery, except for cesarean section.
- For cesarean section surgery, to minimize exposure of the newborn baby to the drug, apply the patch one hour prior to cesarean section.

2.2 Continuation of Therapy

Should the patch become displaced, it should be discarded, and a fresh one placed on the hairless area behind the other ear.

Motion Sickness

If therapy is required for longer than 3 days, the first patch should be removed and a fresh one placed on the hairless area behind the other ear.

Post Operative Nausea and Vomiting

For perioperative use, the patch should be kept in place for 24 hours following surgery at which time it should be removed and discarded.

3 DOSAGE FORMS AND STRENGTHS

The scopolamine transdermal system is a tan-colored circular flat patch which contains 1.3 mg of scopolamine base and is formulated to deliver *in-vivo* approximately 1 mg of scopolamine over 3 days.

4 CONTRAINDICATIONS

Scopolamine transdermal system is contraindicated in the following populations:

- Patients with angle closure glaucoma. *[see Adverse Reactions (6)]*
- Persons who are hypersensitive to the drug scopolamine or other belladonna alkaloids or to any ingredient or component in the formulation or delivery system. *[see Drug Interactions (7) and Description (11)]*

5 WARNINGS AND PRECAUTIONS

5.1 Open Angle Glaucoma

Patients currently being treated for Open Angle Glaucoma

Glaucoma therapy in patients with open angle glaucoma should be monitored and may need to be adjusted during scopolamine transdermal system use, as the mydriatic effect of scopolamine may cause an increase in intraocular pressure. Patients should be advised to remove the patch immediately and promptly contact a physician in the event that they experience symptoms of acute angle closure glaucoma (pain and reddening of the eyes, accompanied by dilated pupils).

5.2 Temporary Dilation of the Pupil

Scopolamine can cause temporary dilation of the pupils and blurred vision if it comes in contact with the eyes.

Patients should be strongly advised to wash their hands thoroughly with soap and water immediately after handling the patch. *[see Adverse Reactions (6)]* In addition, it is important that used patches be disposed of properly to avoid contact with children or pets. *[see How Supplied/Storage and Handling (16)]*

5.3 Preexisting Gastrointestinal or Urinary Bladder Obstructions

Scopolamine transdermal system should be used with caution in patients with pyloric obstruction or urinary bladder neck obstruction. Caution should be exercised when administering an antiemetic or anticholinergic drug, including scopolamine transdermal system, to patients suspected of having intestinal obstruction.

Patients should be instructed to remove the patch if they develop any difficulties in urinating. *[see Adverse Reactions (6)]*

5.4 History of Seizures or Psychosis

Scopolamine transdermal system should be used with caution in patients with a history of seizures or psychosis since scopolamine can potentially aggravate both disorders.

5.5 Idiosyncratic Reactions

Idiosyncratic reactions may occur with ordinary therapeutic doses of scopolamine. The most serious of these that have been reported are: acute psychosis, including confusion, agitation, speech disorder, hallucinations, paranoia, and delusions. *[see Adverse Reactions (6)]*

5.6 Specific Populations

Pediatric

A safe and effective dose has not been established in the pediatric population *[see Use in Specific Populations (8.4)]*. Children are particularly susceptible to the side effects of belladonna alkaloids; including mydriasis, hallucinations, amblyopia, and drug withdrawal syndrome. Neurologic and psychiatric adverse reactions, such as hallucinations, amblyopia and mydriasis have also been reported when one half or one quarter of a patch has been applied.

Elderly

Scopolamine transdermal system should be used with caution in the elderly because of the increased likelihood of CNS effects, such as hallucinations, confusion, dizziness and drug withdrawal syndrome. Clinical trials of scopolamine transdermal system did not include sufficient number of subjects aged 65 years and older to determine if they respond differently from younger subjects. *[see Use in Specific Populations (8.5)]*

Renal and Hepatic Impaired

Scopolamine transdermal system should be used with caution in individuals with impaired renal or hepatic functions because of the increased likelihood of CNS effects. Scopolamine transdermal system has not been studied in these populations. *[see Use in Specific Populations (8.6)]*

5.7 Safety Hazards

Drowsiness

Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, patients should be warned of the possibility and cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery.

Disorienting Effects

Patients who expect to participate in underwater sports should be cautioned regarding the potentially disorienting effects of scopolamine. *[see Patient Counseling Information (17)]*

5.8 MRI Skin Burns

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

6 ADVERSE REACTIONS

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 clinical practice.

Motion Sickness

In motion sickness clinical studies of scopolamine transdermal system, the most frequent adverse reaction was dry mouth. This occurred in about two thirds of patients on drug. A less frequent adverse drug reaction was drowsiness, which occurred in less than one sixth of patients on drug. Transient impairment of eye accommodation, including blurred vision and dilation of the pupils, was also observed.

Post-Operative Nausea and Vomiting

In a total of five clinical studies in which scopolamine transdermal system was administered perioperatively to a total of 461 patients where safety was assessed, dry mouth was the most frequently reported adverse drug reaction, which occurred in approximately 29% of patients on drug. Dizziness was reported by approximately 12% of patients on drug. Other adverse drug reactions reported from these studies, with a frequency of ≥3% of patients treated with scopolamine transdermal system and with a frequency higher than placebo were, in descending order: somnolence, urinary retention, agitation/restlessness, visual impairment, confusion, mydriasis and pharyngitis (see Table 6.1).

Table 6-1 PONV: Adverse Drug Reactions in ≥3% of Patients

	Scopolamine transdermal system (N=461)		Placebo (N=457)	
	n	%	n	%
Adverse Drug Reactions	303	65.7	259	56.7
Dry Mouth	133	28.9	72	15.8
Dizziness	57	12.4	33	7.2
Somnolence	36	7.8	16	3.5
Urinary Retention	33	7.2	30	6.6
Agitation	28	6.1	20	4.4
Visual Impairment	23	5.0	12	2.6
Confusion	18	3.9	14	3.1
Mydriasis	16	3.5	2	0.4
Pharyngitis	15	3.3	10	2.2

6.2 Postmarketing Experience

The following adverse drug reactions, further to those reported from clinical trials, have been identified during postapproval use of scopolamine transdermal system. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to confirm a definite causal relationship.

In worldwide marketing with scopolamine transdermal system, the following adverse drug reactions were reported by body system.

Psychiatric disorders: acute psychosis including: hallucinations, disorientation, and paranoia.

Nervous system disorders: headache, amnesia, coordination abnormalities, speech disorder, disturbance in attention, restlessness.

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General disorders and administration site conditions: application site burning.

Eye disorders: dry eyes, eye pruritus, angle closure glaucoma, amblyopia, eyelid irritation.

Skin and subcutaneous tissue disorders: rash generalized, skin irritation, erythema.

Renal and urinary disorders: dysuria.

Ear and Labyrinth Disorders: vertigo.

6.3 Drug Withdrawal/Post-Removal Symptoms

Symptoms such as dizziness, nausea, vomiting, abdominal cramps, sweating, headache, mental confusion, muscle weakness, bradycardia and hypotension may occur following abrupt discontinuation of anticholinergic drugs such as scopolamine transdermal system. Similar symptoms, including disturbances of equilibrium, have been reported in some patients following discontinuation of use of the scopolamine transdermal system. These symptoms usually do not appear until 24 hours or more after the patch has been removed. These symptoms can be severe and may require medical intervention. Some symptoms may be related to adaptation from a motion environment to a motion-free environment.

These symptoms can be severe and may require medical intervention.

7 DRUG INTERACTIONS

The absorption of oral medications may be decreased during the concurrent use of scopolamine because of decreased gastric motility and delayed gastric emptying. *[see Warnings and Precautions (5.5)]*

Scopolamine should be used with caution in patients taking other drugs that are capable of causing CNS effects such as sedatives, tranquilizers, or alcohol. Special attention should be paid to potential interactions with drugs having anticholinergic properties; e.g., other belladonna alkaloids, antihistamines (including meclizine), tricyclic antidepressants, and muscle relaxants.

In vitro studies indicated that the potential for scopolamine to alter the pharmacokinetics of other concomitant medications through inhibition of CYP 1A2, 2C8, 2C9, 2C19, 2D6 and 3A4 or induction of CYP 1A2 and 3A4 is low; however, *in vivo* studies have not been conducted. *[see Clinical Pharmacology (12.3)]*

7.1 Laboratory Test Interactions

Scopolamine will interfere with the gastric secretion test.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Based on data from one prospective study of scopolamine transdermal system in cesarean delivery, the rate of newborn adverse events in both the scopolamine transdermal system and placebo groups were the same.

The rates were 10.5% (12 events in 114 newborns) in both treatment groups. None of these events were considered life threatening or drug related. Jaundice was the only adverse event occurring more frequently with scopolamine transdermal system than placebo: 9 events (7.9%) versus 2 events (1.8%) (p=0.031). Jaundice, a common occurrence in newborns, resolved with ultraviolet light and did not prolong the hospital stay.

There are no adequate and well-controlled studies of scopolamine transdermal system use during pregnancy. In animal reproduction studies, when pregnant rats and rabbits received scopolamine hydrobromide by daily intravenous injection, no adverse effects were observed in rats. An embryotoxic effect was observed in rabbits at doses producing plasma levels approximately 100 times the levels achieved in humans using a transdermal system. Scopolamine transdermal system should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus and the mother.

8.2 Labor and Delivery

During a clinical study among women undergoing cesarean section treated with scopolamine transdermal system in conjunction with epidural anesthesia and opiate analgesia, no evidence of CNS depression was found in newborns. *[see Clinical Studies (14.2)]* Scopolamine administered parenterally to rats and rabbits at doses higher than the dose delivered by scopolamine transdermal system did not affect uterine contractions or increase the duration of labor. Scopolamine does cross the placenta.

8.3 Nursing Mothers

Scopolamine is excreted in human milk. Caution should be exercised when scopolamine transdermal system is administered to a nursing woman.

8.4 Pediatric Use

A safe and effective dose has not been established in the pediatric population. *[see Warnings and Precautions (5.6)]*

8.5 Geriatric Use

Scopolamine transdermal system should be used with caution in the elderly because of the increased likelihood of CNS effects, such as hallucinations, confusion and dizziness. Clinical trials of scopolamine transdermal system did not include sufficient number of subjects aged 65 years and older to determine if they respond differently from younger subjects. *[see Warnings and Precautions (5.6)]*

8.6 Renal or Hepatic Impairment

Scopolamine transdermal system should be used with caution in individuals with impaired renal or hepatic functions because of the increased likelihood of CNS effects. *[see Warnings and Precautions (5.6)]*

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance Class

Scopolamine is not a controlled substance.

9.2 Abuse

Scopolamine is an antagonist at muscarinic receptors in the cholinergic system. Drugs in this class are not known to have significant abuse potential in humans.

9.3 Dependence

Abrupt termination of scopolamine transdermal system may result in withdrawal symptoms such as dizziness, nausea, vomiting, abdominal cramps, sweating, headache, mental confusion, muscle weakness, bradycardia and hypotension. *[see Adverse Reactions (6.3) and Overdosage (10)]*. These withdrawal symptoms indicate that anticholinergic drugs, like scopolamine may produce physical dependence. These symptoms can be severe and may require medical intervention.

10 OVERDOSAGE

Because strategies for the management of drug overdose continually evolve, it is strongly recommended that a poison control center be contacted to obtain up-to-date information regarding the management of scopolamine transdermal system overdose. The prescriber should be mindful that antidotes used routinely in the past may no longer be considered optimal treatment.

For example, physostigmine, used more or less routinely in the past, is seldom recommended for the routine management of anticholinergic syndromes.

Until up-to-date authoritative advice is obtained, routine supportive measures should be directed to maintaining adequate respiratory and cardiac function.

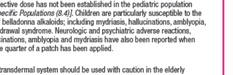
The signs and symptoms of anticholinergic toxicity include: lethargy, somnolence, coma, confusion, agitation, hallucinations, convulsion, visual disturbance, dry flushed skin, dry mouth, decreased bowel sounds, urinary retention, tachycardia, hypertension, and supraventricular arrhythmias. These symptoms can be severe and may require medical intervention.

In cases of toxicity remove the patch. Serious symptomatic cases of overdosage involving multiple patch applications and/or ingestion may be managed by initially ensuring the patient has an adequate airway, and supporting respiration and circulation. This should be rapidly followed by removal of all patches from the skin and the mouth. If there is evidence of patch ingestion, gastric lavage, endoscopic removal of swallowed patches, or administration of activated charcoal should be considered, as indicated by the clinical situation. In any case where there is serious overdosage or signs of evolving acute toxicity, continuous monitoring of vital signs and ECG, establishment of intravenous access, and administration of oxygen are all recommended.

The symptoms of overdose/toxicity due to scopolamine should be carefully distinguished from the occasionally observed syndrome of withdrawal. *[see Adverse Reactions (6.3)]* Although mental confusion and dizziness may be observed with both acute toxicity and withdrawal, other characteristic findings differ: tachyarrhythmias, dry skin, and decreased bowel sounds suggest anticholinergic toxicity, while bradycardia, headache, nausea and abdominal cramps, and sweating suggest post-removal withdrawal. Obtaining a careful history is crucial to making the correct diagnosis.

11 DESCRIPTION

The scopolamine transdermal system is a circular flat patch designed for continuous release of scopolamine following application to an area of intact skin on the head, behind the ear. Each system contains 1.3 mg of scopolamine base. Scopolamine is α -(hydroxymethyl) benzeneacetic acid 9-methyl-3-oxa-9-azatricyclo [3.3.1.0^{2,4}] non-7-yl ester. The empirical formula is $C_{17}H_{21}NO_4$ and its structural formula is:



Scopolamine is a white to almost white, crystalline powder that has a molecular weight of 303.35 and a pKa of 7.55–7.81. The scopolamine transdermal system is a film 0.2 mm thick and 2.5 cm^2, with four layers. Proceeding from the visible surface towards the surface attached to the skin, these layers are: (1) a backing layer of tan-colored, aluminized, polyester film; (2) a drug reservoir of scopolamine, crospovidone, isopropyl palmitate, light mineral oil, and polyisobutylene; (3) an ethylene vinyl acetate copolymer membrane that controls the rate of delivery of scopolamine from the system to the skin surface; and (4) an adhesive formulation of crospovidone, isopropyl palmitate, light mineral oil, polyisobutylene, and scopolamine. A protective peel strip of siliconized polyester, which covers the adhesive layer, is removed before the system is used. The inactive components, crospovidone (3.63 mg), isopropyl palmitate (1.81 mg), light mineral oil (11.42 mg) and polyisobutylene (16.83 mg), are not released from the system.

Cross section of the system:

Backing Layer	
Drug Reservoir	
Rate-Controlling Membrane	
Contact Adhesive	
Protective Peel Strip	

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Scopolamine, a belladonna alkaloid, is an anticholinergic agent. Scopolamine acts: i) as a competitive inhibitor at postganglionic muscarinic receptor sites of the parasympathetic nervous system, and ii) on smooth muscles that respond to acetylcholine but lack cholinergic innervation. It has been suggested that scopolamine acts in the central nervous system (CNS) by blocking cholinergic transmission from the vestibular nuclei to higher centers in the CNS and from the reticular formation to the vomiting center. Scopolamine can inhibit the secretion of saliva and sweat, decrease gastrointestinal secretions and motility, cause drowsiness, dilate the pupils, increase heart rate, and depress motor function.

12.3 Pharmacokinetics

The pharmacokinetics of scopolamine delivered via the system are due to the characteristics of both the drug and dosage form. The system is formulated to deliver *in-vivo* approximately 1 mg of scopolamine at an approximately constant rate to the systemic circulation over 3 days. Upon application to the postauricular skin, an initial priming dose of scopolamine is released from the adhesive layer to saturate skin-binding sites. The subsequent delivery of scopolamine to the blood is determined by the rate controlling membrane and is designed to produce stable plasma levels in a therapeutic range. Following removal of the used system, there is some degree of continued systemic absorption of scopolamine bound in the skin layers.

Absorption

Scopolamine is well absorbed percutaneously. Following application to the skin behind the ear, circulating plasma levels are detected within 4 hours with peak levels being obtained, on average, within 24 hours. The average plasma concentration produced is 87 pg/mL (0.28 nM) for free scopolamine and 354 pg/mL for total scopolamine (free + conjugates).

Distribution

The distribution of scopolamine is not well characterized. It crosses the placenta and the blood brain barrier and may be reversibly bound to plasma proteins.

Metabolism and Excretion

The exact elimination pattern of scopolamine has not been determined. Following patch removal, plasma levels of scopolamine decline in a log linear fashion with an observed half-life of 9.5 hours. Less than 10% of the total dose is excreted in the urine as the parent drug and metabolites over 108 hours. Scopolamine is extensively metabolized and conjugated with less than 5% of the total dose appearing unchanged in the urine. The enzymes responsible for metabolizing scopolamine are unknown.

Drug Interaction

An *in vitro* study using human hepatocytes examined the induction of CYP1A2 and CYP3A4 by scopolamine. Scopolamine did not induce CYP1A2 and CYP3A4 isoenzymes at the concentrations up to 10 nM.

In an *in vitro* study using human liver microsomes which evaluated the inhibition of CYP1A2, 2C8, 2C9, 2C19, 2D6 and 3A4, scopolamine did not inhibit these cytochrome P450 isoenzymes at the concentrations up to 1 mcM.

13 NONCLINICAL PHARMACOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been conducted to evaluate the carcinogenic potential of scopolamine. The mutagenic potential of scopolamine has not been evaluated.

Fertility studies were performed in female rats and revealed no evidence of impaired fertility or harm to the fetus due to scopolamine hydrobromide administered by daily subcutaneous injection. Maternal body weights were reduced in the highest-dose group (plasma level approximately 500 times the level achieved in humans using a transdermal system). However, fertility studies in male animals were not performed.

14 CLINICAL STUDIES

14.1 Motion Sickness

In 195 adult subjects of different racial origins who participated in clinical efficacy studies at sea or in a controlled motion environment, there was a 75% reduction in the incidence of motion-induced nausea and vomiting.

14.2 Post-Operative Nausea and Vomiting

In two pivotal clinical efficacy studies in 391 adult female patients undergoing cesarean section or gynecological surgery with anesthesia and opiate analgesia, 66% of those treated with scopolamine transdermal system (compared to only 46% of those receiving placebo) reported no retching/vomiting within the 24-hour period following administration of anesthesia/opiate analgesia. When the need for additional antiemetic medication was assessed during the same period, there was no need for medication in 76% of patients treated with scopolamine transdermal system as compared to 59% of placebo-treated patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

The scopolamine transdermal system is a tan-colored circular patch, 2.5 cm^2, on a clear, oversized, square peel strip, which is removed prior to use.

Each scopolamine transdermal system contains 1.3 mg of scopolamine and is formulated to deliver *in-vivo* approximately 1 mg of scopolamine over 3 days.

Scopolamine transdermal system is available in packages of four, ten and twenty four patches. Each patch is foil wrapped. Patient instructions are included. *[see Patient Counseling Information (17)]*

- 1 Package (4 patches) NDC 45802-588-84
- 1 Package (10 patches) NDC 45802-588-46
- 1 Package (24 patches) NDC 45802-588-62

Storage

Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature].

Handling

Since scopolamine can cause temporary dilation of the pupils and blurred vision if it comes in contact with the eyes, patients should be strongly advised to wash their hands thoroughly with soap and water immediately after handling the patch. In addition, it is important that used patches be disposed of properly to avoid contact with children or pets.
[see Dosage and Administration (2), Warnings and Precautions (5.2), and Patient Counseling Information (17)]

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Please read this instruction sheet carefully before opening the system package.

Scopolamine Transdermal System 1 mg/3 days

Generic Name: scopolamine, pronounced skoe-POL-a-meen

- Elderly patients should be informed that scopolamine transdermal system may cause a greater likelihood of CNS effects, such as hallucinations, confusion, dizziness and drug withdrawal syndrome and to seek immediate medical care if they become confused, disoriented or dizzy while wearing the patch or after removing.
- Patients should be informed that since scopolamine transdermal system may cause drowsiness, disorientation and confusion they should avoid engaging in activities that require mental alertness such as driving a motor vehicle or operating dangerous machinery.
- Patients who expect to participate in underwater sports should be cautioned regarding the potentially disorienting effects of scopolamine transdermal system.
- Because of the possibility of drowsiness, disorientation and confusion, patients should be informed that they should avoid drinking alcohol.
  In addition, patients should be informed that the following medications should be used with caution when taking scopolamine transdermal system:
  - sedatives or tranquilizers
  - drugs with anticholinergic properties (e.g., other belladonna alkaloids),
  - antihistamines (including meclizine)
  - tricyclic antidepressants
  - muscle relaxants
- Patients with the following conditions should be informed about the chance of developing serious reactions with scopolamine transdermal system:
  - patients with open angle glaucoma (may cause an increase in intraocular pressure)
  - patients with impaired kidney or liver function (increased likelihood of CNS effects)
  - patients with a history of seizures or psychosis (can potentially worsen both disorders)
  - patients with obstruction at the level of the pylorus, which is the outlet of the stomach, or urinary bladder neck obstruction (may cause difficulties in urinating)
  - patients suspected of having intestinal obstruction
  - pregnant or nursing mothers
- Patients should be informed that if they remove the scopolamine transdermal system suddenly before treatment is complete, the following withdrawal symptoms may occur: dizziness, nausea, vomiting, abdominal cramps, sweating, headache, mental confusion, muscle weakness, slow heart rate and low blood pressure. Patients should be instructed to seek immediate medical care if they develop any of these symptoms after removing scopolamine transdermal system.
- Patients should be informed that scopolamine transdermal system can cause temporary dilation of the pupils and blurred vision if it comes in contact with the eyes. Patients should be informed to wash their hands thoroughly with soap and water immediately after handling the patch. In addition, patients should be informed that used patches must be disposed of properly to avoid contact with children or pets.
- Patients should be informed that skin burns have been reported at the patch site in several patients wearing an aluminized transdermal system during a Magnetic Resonance Imaging scan (MRI). Because scopolamine transdermal system contains aluminum, patients should be advised to remove the system before undergoing an MRI.
- Patients should be advised to use only one patch at a time.
- Patients should be advised not to cut the patch.

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FDA-Approved Patient Labeling

PATIENT INFORMATION

Scopolamine transdermal system 1 mg/3 days

Read this Patient Information before you start using scopolamine transdermal system and each time you get a refill. There may be new information.
This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is scopolamine transdermal system?
The scopolamine transdermal system is a prescription medicine used for adults to:

- help prevent nausea and vomiting from motion sickness
- help prevent nausea and vomiting from anesthesia or taking opioid pain medicines after surgery

It is not known if scopolamine transdermal system is safe or effective in children.

Who should not use scopolamine transdermal system?

Do not use scopolamine transdermal system if you:

- have an eye problem called angle closure glaucoma
- if you are allergic to any of the ingredients in scopolamine transdermal system or other medicines called belladonna alkaloids. See the end of this leaflet for a list of the ingredients in scopolamine transdermal system. Ask your doctor if you are not sure.

What should I tell my doctor before using scopolamine transdermal system?

Before you use scopolamine transdermal system, tell your doctor if you:

- are scheduled to have a gastric secretion test
- have glaucoma (increased pressure in the eye)
- have liver or kidney problems
- have problems with your stomach or intestines
- have trouble urinating
- have a history of seizures or psychosis
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if scopolamine transdermal system can harm your unborn baby.
- are breast-feeding or plan to breast-feed. Scopolamine can pass into your breast milk and may harm your baby. Talk to your doctor about the best way to feed your baby if you use scopolamine transdermal system.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Scopolamine transdermal system may affect the way other medicines work, and other medicines may affect how scopolamine transdermal system works. Medicines that you take by mouth may not be absorbed well while you use scopolamine transdermal system.

Especially tell your doctor if you take:

- a sedative or tranquilizer (medicines that make you sleepy)
- an antidepressant medicine
- an anticholinergic medicine, such as an allergy or cold medicine, a medicine to treat bladder or bowel spasms, certain asthma medicines, or other medicines for motion sickness.

Ask your doctor if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of them and show it to your doctor or pharmacist when you get a new medicine.

How should I use scopolamine transdermal system?

Use scopolamine transdermal system exactly as your doctor tells you to use it.
Scopolamine transdermal system is a tan-colored circle shaped patch.
Wear only one patch at any time.

Do not cut the patch.

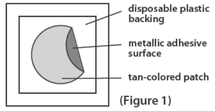
To help prevent nausea and vomiting from motion sickness:

- Apply one scopolamine transdermal system to your skin on a hairless area behind one ear at least 4 hours before the activity to prevent nausea and vomiting.
- If the treatment is needed for longer than 3 days, remove the patch from the hairless area behind your ear. Get a new scopolamine transdermal system and place it on the hairless area behind your other ear.

To help prevent nausea and vomiting after surgery:

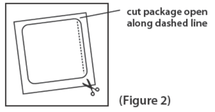
- Follow your doctor's instructions about when to apply scopolamine transdermal system before your scheduled surgery.
- The scopolamine transdermal system should be left in place for 24 hours after surgery. After 24 hours the patch should be removed and thrown away.

Apply scopolamine transdermal system as follows:
Inside the scopolamine transdermal system package, you will find one scopolamine transdermal system. A tan colored patch with a metallic (silver) sticky surface is adhered to a clear disposable backing (See Figure 1).



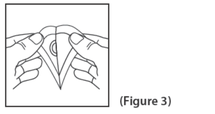
(Figure 1)

1. Select a hairless area of skin behind one of your ears. Avoid areas on your skin that may have cuts, pain or tenderness. Wipe the area of your skin with a clean, dry tissue.
2. Cut along dotted line on the scopolamine transdermal system package to open (See Figure 2).

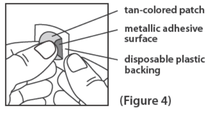


(Figure 2)

3. Remove the clear plastic backing from the tan-colored round patch (See Figure 3).

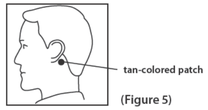

(Figure 3)

4. Avoid touching the metallic adhesive (sticky) surface on the patch with your hands (See Figure 4).



(Figure 4)

5. Apply the metallic adhesive surface of the patch firmly to the dry area of skin behind your ear. The tan-colored side of the patch should be facing up and showing (See Figure 5). Wash your hands with soap and water right away after applying the patch, so that any medicine from the patch that gets on your hands will not get into your eyes.



(Figure 5)

After removing the patch, be sure to wash your hands and the area behind your ear thoroughly with soap and water. Note that the used patch will still contain some of the active ingredient after use. To avoid accidental contact or ingestion by children or pets, fold the used patch in half with the sticky side together. Dispose in the trash out of the reach of children and pets.
If you use too much scopolamine transdermal system, call your doctor or local poison control center, or go to the nearest hospital emergency room right away.

What should I avoid while using scopolamine transdermal system?

- You should not drink alcohol while using scopolamine transdermal system. It can increase your chances of having serious side effects.
- You should not drive, operate heavy machinery, or do other dangerous activities until you know how scopolamine transdermal system affects you.
- You should not use scopolamine transdermal system during a Magnetic Resonance Imaging scan (MRI). Remove scopolamine transdermal system before undergoing an MRI; it can cause your skin to burn.
- You should be careful if you use scopolamine transdermal system while you participate in watersports because you may feel lost or confused (disoriented).
- Limit contact with water while swimming and bathing because the scopolamine transdermal system may fall off. If the patch falls off, throw it away and apply a new one on the hairless area behind your other ear.

What are the possible side effects of scopolamine transdermal system?

Scopolamine transdermal system may cause serious side effects, including:

- **angle closure glaucoma.** If you have open angle glaucoma and use scopolamine transdermal system, remove the patch and call a doctor right away if you get pain and reddening of your eyes with an increase in the size of your pupil (the small dark circle in the eye).
- **temporary increase in the size of your pupil and blurry vision,** especially if scopolamine transdermal system comes in contact with your eyes
- **difficulties in urinating**
- **difficulties in food passing from the stomach to the small intestines, which may cause abdominal pain, nausea or vomiting.**
- **worsening of seizures.** Tell your doctor about any worsening of seizures while using scopolamine transdermal system.
- **an unusual reaction called acute psychosis:** Tell your doctor if you have any of these symptoms:
  - confusion
  - agitation
  - rambling speech
  - hallucinations (seeing or hearing things that are not there)
  - paranoid behaviors and delusions (false belief in something)

Page 2

FLAT SIZE = 11.875" x 11.875" FOLD SIZE = 3.0" x 2.0"

- **skin burns at the site of the patch.** This can happen during a medical test called a Magnetic Resonance Imaging scan (MRI). Scopolamine transdermal system contains aluminum and should be removed from your skin before you have an MRI.

The most common side effects of using scopolamine transdermal system include:

- dry mouth
- drowsiness
- disorientation (confusion)
- blurred vision
- pharyngitis
- memory trouble
- dizziness
- restlessness
- agitation
- problems urinating
- skin rashes or redness, application site burning
- dry itchy, or reddened whites of the eyes, and eye pain

Symptoms when removing scopolamine transdermal system. Some people may have certain symptoms 24 hours or more after removing scopolamine transdermal system. These symptoms may include:

- dizziness
- nausea
- vomiting
- headache
- problems with balance and walking
- decrease in blood pressure
- muscle weakness
- decrease in heart rate

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of scopolamine transdermal system. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. To report SUSPECTED ADVERSE REACTIONS, contact Perrigo Company at 1-866-634-9120, or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

How should I store scopolamine transdermal system?

- Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature].
- **Keep scopolamine transdermal system and all medicines out of reach of children.**

General Information about scopolamine transdermal system

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use scopolamine transdermal system for a condition for which it was not prescribed. Do not give scopolamine transdermal system to other people, even if they have the same symptoms you have. It may harm them.

This patient information leaflet summarizes the most important information about scopolamine transdermal system. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about scopolamine transdermal system that is written for the health professionals.

For more information, call 1-866-634-9120.

What are the ingredients in the scopolamine transdermal system patch?

Active ingredient: Scopolamine

Inactive ingredients: crospovidone, isopropyl palmitate, light mineral oil, polyisobutylene, ethylene vinyl acetate copolymer and aluminized polyester film

Mfd. by:
AVEVA Drug Delivery Systems
An APOTEX Company
Miramar, FL 33025

Distributed By
Perrigo®
Allegan, MI 49010 • www.perrigo.com

3002166 Rev 11-14

S&BOD RC J/4

NO COPY

NO COPY

NO COPY

NO COPY

12-02-14

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78830

LABELING REVIEWS

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

(APPROVAL SUMMARY)

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (5th Cycle)

ANDA Number:	ANDA 078830
Date of Submission:	December 4, 2014
Applicant:	Perrigo R&D Co.
Established Name and Strength:	Scopolamine Transdermal System, 1 mg/3 days
Proposed Proprietary Name:	None

Labeling Comments below are considered:

☐ Minor Deficiency *

* Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.

☒ No Comments **(**Labeling Approval Summary)

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

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated December 4, 2014.

Please continue to monitor available labeling resources such as 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.

REVISIONS NEEDED POST APPROVAL? Yes
The sponsor committed that they will revise "Contents – 1 Patch" to read "Content – 1 Patch" as requested and will submit the revised pouch in the first annual report.

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER: No

Review Summary

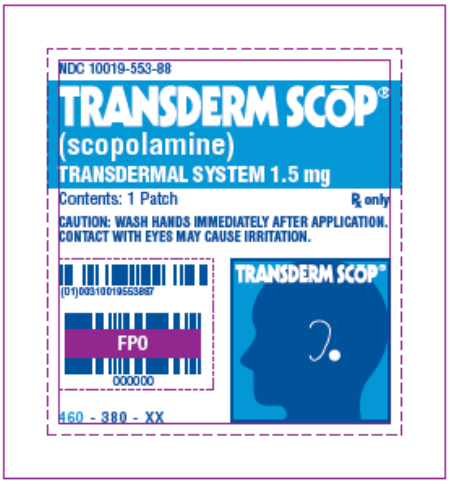
Labeling Submitted	Date submitted	Final or Draft	Recommendation
POUCH – 1 Patch	12/4/2014	FINAL	AC for AP
CARTON – 4 Pouches	12/4/2014	FINAL	AC for AP

INSERT	12/4/2014	FINAL	AC for AP
PATIENT INFORMATION	12/4/2014	FINAL (10 pts)	AC for AP
SPL -DLPE	12/4/2014	NA	AC

FOR THE RECORD: (Part of the information is from the review performed by Theresa Liu.)

1. MODEL LABELING

This review is based on the labeling of Transderm Scop® of Novartis Consumer Health Inc. (NDA 017874/S-038), approved April 30, 2013. This "Prior Approval" supplemental new drug application provides for the conversion of the package insert to Physician's Labeling Rule (PLR) format. NDA 017874/S-040, approved May 15, 2013 was for an alternate manufacturing process, thus does not affect the generic labeling.



150%

TEAR ALONG LINE TO OPEN

Each patch contains 1.5 mg scopolamine formulated to deliver *in vivo* approximately 1 mg over 3 days. The inactive components are light mineral oil, polyisobutylene, polypropylene and aluminized polyester film.

Dosage and Administration:

1. Before applying patch, wash and dry hands thoroughly.
2. Use only one patch at a time.
3. Remove and discard clear plastic backing from the patch.
4. Apply to the hairless area behind one ear as indicated in accompanying prescribing information.
5. Wash and dry hands thoroughly after application.

See accompanying prescribing information for details.

Caution: May cause drowsiness, blurred vision. To avoid possible burns, remove Transderm Scōp® before undergoing an MRI (Magnetic Resonance Imaging) procedure.

Keep this and all medication out of reach of children.

FOIL SEALED FOR YOUR PROTECTION.

DO NOT USE IF SEAL IS BROKEN.

Store at controlled room temperature between 20°C – 25°C (68°F – 77°F).

Baxter NOVARTIS

Marketed by **Baxter Healthcare Corporation**
Deerfield, IL 60015 USA
Manufactured by ALZA Corporation
Vacaville, CA 95688
for **Novartis Consumer Health, Inc.**
Parsippany, NJ 07054-0622
©2011

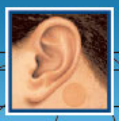
460-380-XX
XXXXXXX

TRANSDERM SCŌP®
(scopolamine) TRANSDERMAL SYSTEM 1.5 mg

NDC 0067-4345-04
NSN 6505-01-456-2380

TRANSDERM SCŌP®

(scopolamine) TRANSDERMAL SYSTEM 1.5 mg



Formulated delivery of approximately 1 mg over three days

MOTION SICKNESS & POST-OPERATIVE NAUSEA & VOMITING PREVENTION PATCHES

4 PATCHES Rx ONLY

FPO 0067 4345 04 0

TRANSDERM SCŌP®
(scopolamine) TRANSDERMAL SYSTEM 1.5 mg

TRANSDERM SCŌP®
(scopolamine) TRANSDERMAL SYSTEM 1.5 mg

Each patch contains 1.5 mg scopolamine formulated to deliver *in vivo* approximately 1 mg over 3 days. The inactive components are light mineral oil, polyisobutylene, polypropylene and aluminized polyester film.

Dosage and Administration:

1. Before applying patch, wash and dry hands thoroughly.
2. Use only one patch at a time.
3. Remove and discard clear plastic backing from the patch.
4. Apply to the hairless area behind one ear as indicated in accompanying prescribing information.
5. Wash and dry hands thoroughly after application.

See accompanying prescribing information for details.

CONTENTS–4 PATCHES

xxxxxxx

Caution: May cause drowsiness, blurred vision. To avoid possible burns, remove Transderm Scōp® before undergoing an MRI (Magnetic Resonance Imaging) procedure.

Keep this and all medication out of reach of children.

Store at controlled room temperature between 20°C – 25°C (68°F – 77°F).

FOIL-SEALED FOR YOUR PROTECTION. DO NOT USE IF SEAL IS BROKEN.

Mfd. by:
ALZA Corporation
Vacaville, CA 95688

Dist. by:
Novartis Consumer Health, Inc.
Parsippany, NJ 07054-0622
©2011

Questions or Comments?
call 1-800-452-0051

www.transderminscop.com

NOVARTIS

FPO CODE 128

NOTE1: The RLD contains 1.5 mg of active ingredient "scopolamine" while this ANDA product contains 1.3 mg of scopolamine. Both have the same transdermal delivery system (Reservoir system). However, the "Pharmacokinetic" is identical to each other per the insert labeling as follows. The drug reservoir layer of the system has different inactive ingredients from those of RLD.

Pharmacokinetics

Scopolamine's activity is due to the parent drug. The pharmacokinetics of scopolamine delivered via the system are due to the characteristics of both the drug and dosage form. The system is (b) (4) to deliver in-vivo approximately 1 mg of scopolamine at an approximately constant rate to the systemic circulation over 3 days. Upon application to the post-auricular skin, an initial priming dose of scopolamine is released from the adhesive layer to saturate skin binding sites. The subsequent delivery of scopolamine to the blood is determined by the rate controlling membrane and is designed to produce stable plasma levels in a therapeutic range. Following removal of the used system, there is some degree of continued systemic absorption of scopolamine bound in the skin layers.

Absorption: Scopolamine is well-absorbed percutaneously. Following application to the skin behind the ear, circulating plasma levels are detected within 4 hours with peak levels being obtained, on average, within 24 hours. The average plasma concentration produced is 87 pg/mL for free scopolamine and 354 pg/mL for total scopolamine (free + conjugates).

NOTE2: The former reviewer, Theresa Liu, forwarded this comment "To avoid confusion, we suggest relocating "1.3 mg" to the side panel, and replace it with "1 mg/3 days" as your product strength expression.' to the sponsor and the sponsor complied with this comment.

MedWatch – No Information (12/17/2014)

2. USP MONOGRAPH (checked on 12/17/2014)
   Scopolamine Transdermal System is not the subject of USP Monograph and no information was found in the PF.

3. PATENTS AND EXCLUSIVITIES (checked on 12/17/2014)
   There are no unexpired patents or exclusivities.

4. INACTIVE INGREDIENTS:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert IS *consistent* with the listing of inactive ingredients found in the statement of components and composition.

Components and Composition

(b) (4)

[redacted] (b) (4)

NOTE: Contains a backing layer of **aluminized,polyester film**. The container, carton and PI and PPI contains "precaution" information regarding skin burning during the MRI procedure due to the "aluminium" contained in the patch system, i.e. recommendation of removal of this system from the skin before MRI.

5. MANUFACTURING FACILITY
Aveva Drug Delivery Systems, Inc.
3250 Commerce Parkway
An Apotex Co. Company
Miramar, FL 33025

Manufactured for: Perrigo R&D Company Allegan, MI 49010

6. FINISHED PRODUCT DESCRIPTION:
RLD: tan-colored circular patch, 2.5 cm^2, on a clear, oversized, hexagonal peel strip.
ANDA: [redacted] (b) (4) . Insert – "tan-colored circular patch, 2.5 cm^2, on a clear, oversized, [redacted] (b) (4) peel strip".

NOTE: Either RLD or ANDA does not contain any identification information (e.g. name and strength) on the back of the patch.

7. STORAGE CONDITIONS AND DISPENSING RECOMMENDATIONS
RLD: "The system should be stored at controlled room temperature between 20°C - 25°C (68°F - 77°F)." Label: "Foil-sealed for your protection. Do not use if seal is broken."
ANDA: "Store at 20 to 25°C (68 to 77°F) [see USP controlled room temperature]."
Label: "Foil-sealed for your protection. Do not use if seal is broken."

8. PRODUCT LINE:
RLD: packages of four patches.
ANDA: one carton of 4 patches, 10 patches, and 24 patches

9. CONTAINER/CLOSURE SYSTEM:
Each patch is [redacted] (b) (4)

10. PATIENT PACKAGE INSERT – Yes

11. RELATED APPLICATIONS - None

12. SPL DATA ELEMENTS – Acceptable

13. CITIZENS PETITION/PROPRIETARY NAME/CONSULTS - None \

14. SPECIAL CONSIDERATION

We forwarded the following comment regarding pouch to the sponsor and the sponsor responded to the Agency's comment as follows. We will accept the sponsor's proposal.

COMMENT:

We strongly recommend that you replace the illustration of the scissors with instruction for tearing the patch. We believe that it may reduce inadvertent cutting of the patch while opening the pouch.

RESPONSE: See below.

Perrigo acknowledges that the Agency strongly recommends replacement of the illustration of the scissors on the pouch with instruction for tearing the pouch to possibly reduce inadvertent cutting of the patch while opening the pouch.

Since the time of original ANDA submission on ANDA 78830, the scissor-cut illustration has been a part of the Perrigo labeling. Perrigo received one labeling deficiency dated January 01, 2011 and no comments/concerns regarding the scissor-cut illustration were raised at that time. No labeling deficiencies were issued for the Completed Response letter dated June 03, 2013.

Due to the established control standards described above to prevent the inadvertent cutting of the patch when opening the pouch, Perrigo proposes to retain the illustration of the scissors on the pouch material.

Perrigo is committed to producing quality drug products and will monitor the commercial use of the Scopolamine Transdermal System and respond appropriately to promptly resolve any quality issue identified with this product or its packaging.

Date of Review: December 17, 2014

Primary Reviewer: Chan Park

Team Leader: Lisa Kwok

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (4th Cycle)

ANDA Number:	ANDA 078830
Date of Submission:	March 14, 2014
Applicant:	Perrigo R&D Co.
Established Name and Strength:	Scopolamine Transdermal System, 1 mg/3 days
Proposed Proprietary Name:	None

Labeling Comments below are considered:

☒ Minor Deficiency *

* Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.

☐ 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 April 28, 2014, based on your submission dated March 14, 2014.

1. GENERAL
   a. Revise the drug product name to read "Scopolamine Transdermal System" in all labeling pieces.
   b. Please revise the storage statement to read "Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]".

2. Pouch
   a. We strongly recommend that you replace the illustration of the scissors with instruction for tearing the patch. We believe that it may reduce inadvertent cutting of the patch while opening the pouch.
   b. Revise to read "Content – 1 Patch" rather than "Contents – 1 Patch".
   c. Back Panel, Caution:
      Revise to read "…burns, remove the scopolamine transdermal system before…" (b) (4) (b) (4)

3. Carton – 4 Patches
   a. Revise to read "Motion Sickness and Post-operative Nausea & Vomiting Prevention Patches".
   b. Replace "(b) (4) delivery" with "Formulated delivery".
   c. Revise the fourth bullet in the DOSAGE AND ADMINISTRATION" section to read "Apply to the hairless area behind one ear as indicated in accompanying prescribing

information".

4. Patient Information Leaflet
   Increase the font size to 10 pts, at a minimum, for better readability.

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 your last submitted 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.

REVISIONS NEEDED POST APPROVAL? Yes

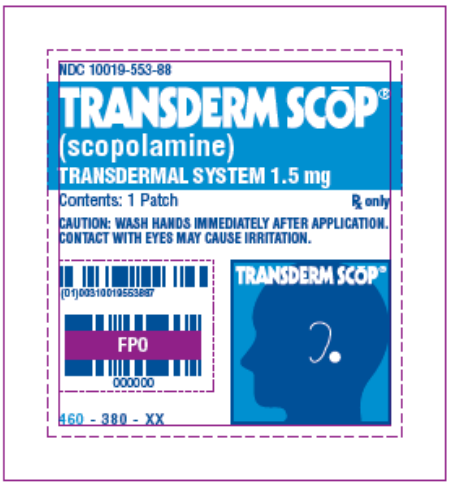
NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER: No

Review Summary

Labeling Submitted	Date submitted	Final or Draft	Recommendation
POUCH – 1 Patch	May 22, 2012	FINAL	NAC for AP
CARTON – 4 Pouches	May 22, 2012	FINAL	NAC for AP
INSERT	March 14, 2014	FINAL (11.4 pts)	NAC for AP
PATIENT INFORMATION	March 14, 2014	FINAL (6.5 pts)	NAC for AP
SPL -DLPE	Not Submitted		

FOR THE RECORD: (Part of the information is from the review performed by Theresa Liu.)

1. MODEL LABELING
   This review is based on the labeling of Transderm Scop® of Novartis Consumer Health Inc. (NDA 017874/S-038), approved April 30, 2013. This "Prior Approval" supplemental new drug application provides for the conversion of the package insert to Physician's Labeling Rule (PLR) format. NDA 017874/S-040, approved May 15, 2013 was for an alternate manufacturing process, thus does not affect the generic labeling.


NDC 10019-553-88
TRANSDERM SCŌP®
(scopolamine)
TRANSDERMAL SYSTEM 1.5 mg
Contents: 1 Patch
℞ only
CAUTION: WASH HANDS IMMEDIATELY AFTER APPLICATION. CONTACT WITH EYES MAY CAUSE IRRITATION.
(01)00310019553887
FPO
000000
TRANSDERM SCŌP®
460 - 380 - XX


TEAR ALONG LINE TO OPEN
Each patch contains 1.5 mg scopolamine formulated to deliver in vivo approximately 1 mg over 3 days. The inactive components are light mineral oil, polyisobutylene, polypropylene and aluminized polyester film.
Dosage and Administration:
1. Before applying patch, wash and dry hands thoroughly.
2. Use only one patch at a time.
3. Remove and discard clear plastic backing from the patch.
4. Apply to the hairless area behind one ear as indicated in accompanying prescribing information.
5. Wash and dry hands thoroughly after application.
See accompanying prescribing information for details.
Caution: May cause drowsiness, blurred vision. To avoid possible burns, remove Transderm Scōp® before undergoing an MRI (Magnetic Resonance Imaging) procedure.
Keep this and all medication out of reach of children.
FOIL SEALED FOR YOUR PROTECTION.
DO NOT USE IF SEAL IS BROKEN.
Store at controlled room temperature between 20°C – 25°C (68°F – 77°F).
Baxter
NOVARTIS
Marketed by Baxter Healthcare Corporation
Deerfield, IL 60015 USA
Manufactured by ALZA Corporation
Vacaville, CA 95688
for Novartis Consumer Health, Inc.
Parsippany, NJ 07054-0622
©2011
460-380-XX
XXXXXXX

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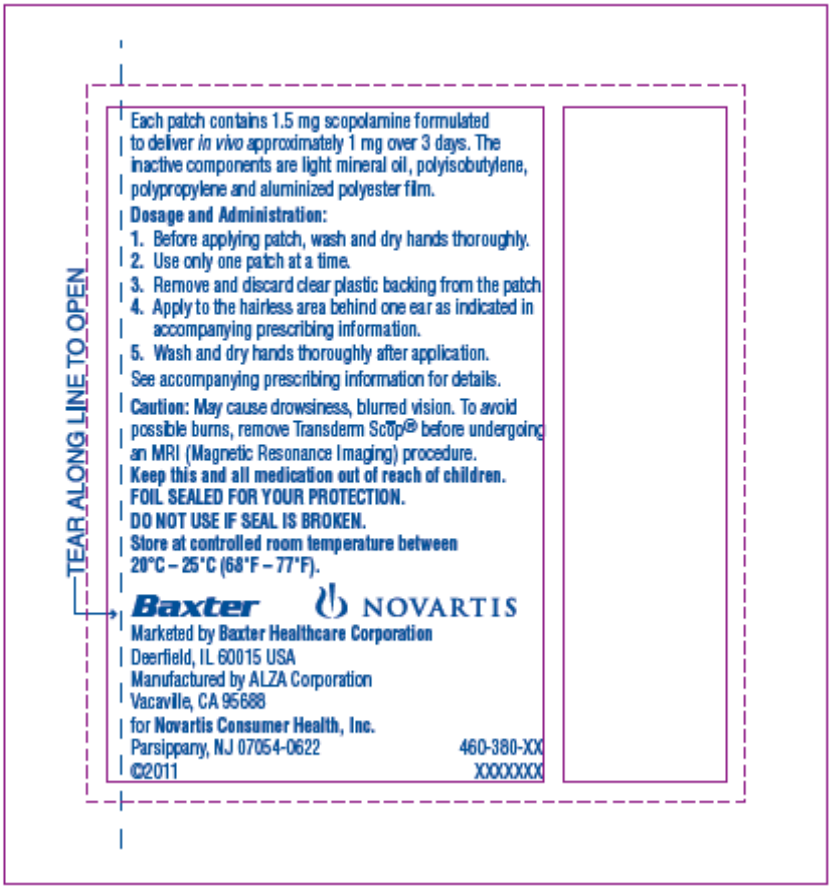
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Store at controlled room temperature between 20°C – 25°C (68°F – 77°F).
Baxter
NOVARTIS
Marketed by **Baxter Healthcare Corporation**
Deerfield, IL 60015 USA
Manufactured by ALZA Corporation
Vacaville, CA 95688
for **Novartis Consumer Health, Inc.**
Parsippany, NJ 07054-0622
©2011
460-380-XX
XXXXXXX

NOTE: The RLD contains 1.5 mg of active ingredient "scopolamine" while this ANDA product contains 1.3 mg of scopolamine. Both have the same transdermal delivery system (Reservoir system). However, the "Pharmacokinetic" is identical to each other per the insert labeling as follows. The drug reservoir layer of the system has different inactive ingredients from those of RLD.

Pharmacokinetics

Scopolamine's activity is due to the parent drug. The pharmacokinetics of scopolamine delivered via the system are due to the characteristics of both the drug and dosage form. The system is (b) (4) to deliver in-vivo approximately 1 mg of scopolamine at an approximately constant rate to the systemic circulation over 3 days. Upon application to the post-auricular skin, an initial priming dose of scopolamine is released from the adhesive layer to saturate skin binding sites. The subsequent delivery of scopolamine to the blood is determined by the rate controlling membrane and is designed to produce stable plasma levels in a therapeutic range. Following removal of the used system, there is some degree of continued systemic absorption of scopolamine bound in the skin layers.

Absorption: Scopolamine is well-absorbed percutaneously. Following application to the skin behind the ear, circulating plasma levels are detected within 4 hours with peak levels being obtained, on average, within 24 hours. The average plasma concentration produced is 87 pg/mL for free scopolamine and 354 pg/mL for total scopolamine (free + conjugates).

NOTE2: The former reviewer, Theresa Liu, forwarded this comment "To avoid confusion, we suggest relocating "1.3 mg" to the side panel, and replace it with "1 mg/3 days" as your product strength expression.' To the sponsor and the sponsor complied with this comment.

MedWatch – No Information (4/9/2014)

2. USP MONOGRAPH (checked on 4/9/2014)
Scopolamine Transdermal System is not the subject of USP Monograph and no information was found in the PF.

3. PATENTS AND EXCLUSIVITIES (checked on 4/9/2014)
There are no unexpired patents or exclusivities.

4. INACTIVE INGREDIENTS:
The listing of inactive ingredients in the DESCRIPTION section of the package insert IS *consistent* with the listing of inactive ingredients found in the statement of components and composition.

Components and Composition

NOTE: Contains a backing layer of **aluminized,polyester film**. The container, carton and PI and PPI contains "precaution" information regarding skin burning during the MRI procedure due to the "aluminium" contained in the patch system, i.e. recommendation of removal of this system from the skin before MRI.

5. MANUFACTURING FACILITY
Aveva Drug Delivery Systems, Inc.
3250 Commerce Parkway
An Apotex Co. Company
Miramar, FL 33025

Manufactured for: Perrigo R&D Company Allegan, MI 49010

6. FINISHED PRODUCT DESCRIPTION:
RLD: tan-colored circular patch, 2.5 cm^2, on a clear, oversized, hexagonal peel strip.
ANDA: (b) (4)

Insert – "tan-colored circular patch, 2.5 cm^2, on a clear, oversized, (b) (4) peel strip".

NOTE: Either RLD or ANDA does not contain any identification information (e.g. name and strength) on the back of the patch.

7. STORAGE CONDITIONS AND DISPENSING RECOMMENDATIONS
RLD: "The system should be stored at controlled room temperature between 20°C - 25°C (68°F - 77°F)." Label: "Foil-sealed for your protection. Do not use if seal is broken."
ANDA: "Store at 20 to 25°C (68 to 77°F) [see USP controlled room temperature]."
Label: "Foil-sealed for your protection. Do not use if seal is broken."

8. PRODUCT LINE:
RLD: packages of four patches.
ANDA: one carton of four patches

9. CONTAINER/CLOSURE SYSTEM:
Each patch is (b) (4)
(b) (4)

10. PATIENT PACKAGE INSERT – Yes (4/9/2014)

11. RELATED APPLICATIONS - None

12. SPL DATA ELEMENTS – Not submitted

13. CITIZENS PETITION/PROPRIETARY NAME/CONSULTS - None (4/9/2014)

Date of Review: April 9, 2014

Primary Reviewer: Chan Park

Acting Team Leader: Jeanne Skanchy

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

/s/

CHAN H PARK
04/29/2014

JEANNE SKANCHY
04/29/2014

(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 078830

Date of Submission: May 22, 2012 (Amendment)

Applicant's Name: Perrigo R&D Company

Established Name: Scopolamine Transdermal Therapeutic System, 1 mg/3 days

Proprietary Name: None proposed

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

REMS Check Boxes
RISK EVALUATION AND MITIGATIONSTRATEGY

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

	FPL	Submission Date	Recommendation
Pouch – 1 patch	yes	May 22, 2012	AC for AP
Carton – 4 Patches	yes	May 22, 2012	AC for AP
PI/PPI (6 pts/6.5 pts)	yes	May 22, 2012	AC for AP
SPL - DLDE	N/A	Not submitted	N/A

REVISIONS NEEDED POST-APPROVAL:

a. Pouch
   i. Revise to read “Content – 1 Patch” rather than “Contents – 1 Patch”.
   ii. Back Panel, Caution:
   Revise to read “…burns, remove the scopolamine transdermal therapeutic system before…” (b) (4)
   (b) (4)

b. Carton – 4 Patches
   See comment a (ii) above.

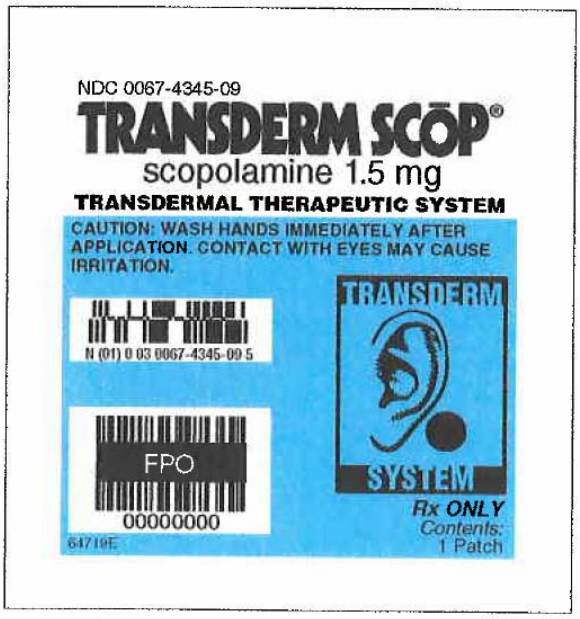
c. Patient Information Leaflet
   Increase the font size to 10 pts, at a minimum, for better readability.

NOTES/QUESTIONS TO THE CHEMIST: None

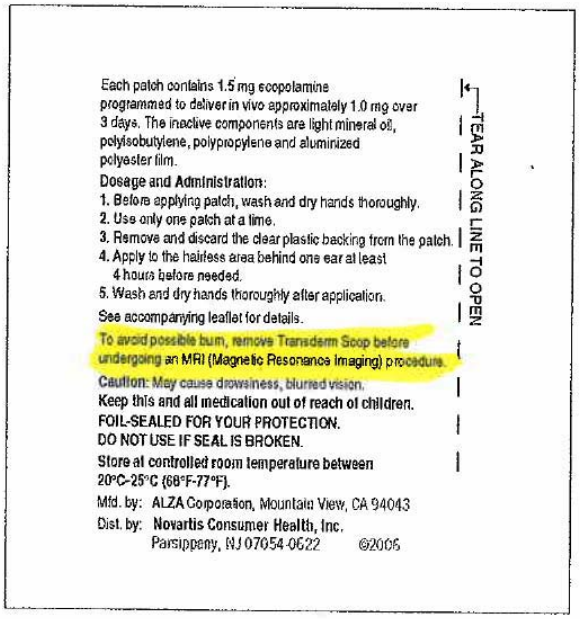
FOR THE RECORD: (Part of the information is from the review performed by Theresa Liu.)

1. MODEL LABELING (as of the 8/16/2012)
   This review is based on the labeling of Transderm Scop® of Novartis Consumer Health Inc. (NDA 017874/S-035, approved January 10, 2007). NDA 017874/S-038 is still pending review with OND.

front



back



NOTE[1]: The RLD contains 1.5 mg of active ingredient "scopolamine" while this ANDA product contains 1.3 mg of scopolamine. Both have the same transdermal delivery system (Reservoir system). However, the "Pharmacokinetic" is identical to each other per the insert labeling as follows. The drug reservoir layer of the system has different inactive ingredients from those of RLD.

Pharmacokinetics

Scopolamine's activity is due to the parent drug. The pharmacokinetics of scopolamine delivered via the system are due to the characteristics of both the drug and dosage form. The system is (b) (4) to **deliver *in-vivo* approximately 1 mg of scopolamine at an approximately constant rate to the systemic circulation over 3 days.** Upon application to the post-auricular skin, an initial priming dose of scopolamine is released from the adhesive layer to saturate skin binding sites. The subsequent delivery of scopolamine to the blood is determined by the rate controlling membrane and is designed to produce stable plasma levels in a therapeutic range. Following removal of the used system, there is some degree of continued systemic absorption of scopolamine bound in the skin layers.

Absorption: Scopolamine is well-absorbed percutaneously. Following application to the skin behind the ear, circulating plasma levels are detected within 4 hours with peak levels being obtained, on average, within 24 hours. **The average plasma concentration produced is 87 pg/mL for free scopolamine and 354 pg/mL for total scopolamine (free + conjugates).**

NOTE[2]: The former reviewer, Theresa Liu, forwarded this comment "To avoid confusion, we suggest relocating "1.3 mg" to the side panel, and replace it with "1 mg/3 days" as your product strength expression.' To the sponsor and the sponsor complied with this comment.

2. USP MONOGRAPH (checked on 8/16/2012)
   Scopolamine Transdermal patch is not the subject of USP Monograph.
   PF: Scopolamine Bromide – Packaging and storage: Preserve in tight, light-resistant containers.

3. PATENTS AND EXCLUSIVITIES (checked on 8/16/2012)
   There are no unexpired patents or exclusivities.

4. INACTIVE INGREDIENTS:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert **IS** consistent with the listing of inactive ingredients found in the statement of components and composition.

   NOTE: Contains a backing layer of aluminized,polyester film. The container, carton and PI contains "precaution" information regarding skin burning during the MRI procedure due to the "aluminium" contained in the patch system, *i.e.* recommendation of removal of this system from the skin before MRI.

5. MANUFACTURING FACILITY
   Aveva Drug Delivery Systems,
   Inc.
   An Apotex Co. Company
   Miramar, FL 33025

   Manufactured for: Perrigo
   R&D Company Allegan,
   MI 49010

6. PRODUCT DESCRIPTION:
   RLD: tan-colored circular patch, 2.5 cm², on a clear, oversized, hexagonal peel strip.
   ANDA: (b) (4) Insert – "tan-colored circular patch, 2.5 cm², on a clear, oversized, (b) (4) peel strip".

7. CONTAINER/CLOSURE SYSTEM:
   Each patch is (b) (4)

8. PRODUCT LINE:
   RLD: packages of four patches.
   ANDA: packages of four patches.

9. STORAGE CONDITIONS:
   RLD: "The system should be stored at controlled room temperature between 20°C - 25°C (68°F - 77°F)."
   ANDA: "Store at 20 to 25°C (68 to 77°F) [see USP controlled room temperature]."

10. DISPENSING RECOMMENDATIONS:
    RLD: Label: "Foil-sealed for your protection. Do not use if seal is broken."
    ANDA: Label: "Foil-sealed for your protection. Do not use if seal is broken."

11. MEDWATCH: (checked 8/16/2012)
    No new alerts or warnings.

12. REMS: (checked 8/16/2012)
    No approved REMS.

13. CITIZEN'S PETITION/SUITABILITY PETITION/PROPRIETARY NAME: None

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Date of Review: August 16, 2012

Primary Reviewer: Chan Park

Team Leader: Koung Lee

Following this page, 16 Pages of Draft Labeling have been Withheld in Full as (b)(4)

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

/s/

CHAN H PARK
08/21/2012

KOUNG U LEE
08/21/2012
For Wm. Peter Rickman

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

ANDA Number: 078830

Date of Submission: February 23, 2007 (Original)

Applicant's Name: Perrigo R&D Company

Established Name: Scopolamine Transdermal Therapeutic System, 1 mg/3 days

Proprietary Name: None proposed

Labeling Deficiencies:

1. GENERAL – You currently list the total content as 1.3 mg. This differs from the reference listed drug's total content of 1.5 mg. To avoid confusion, we suggest relocating "1.3 mg" to the side panel, and replace it with "1 mg/3 days" as your product strength expression.

2. CARTON, CONTAINER/POUCH –
    a. Please see comment 1.
    b. Please delete trailing zeroes (i.e., "1 mg over 3 days" rather than "1.0 mg over 3 days").

3. INSERT
    a. The way you submitted your PDF file of physician insert is incomplete with the top and bottom cut off. Please resubmit the complete insert labeling.
    b. Please replace all "this product" with "Scopolamine transdermal therapeutic system" throughout your insert text.
    c. DESCRIPTION, second paragraph: "…(3)…delivery of scopolamine from…" [missing 'scopolamine'].

Revise your labeling, as instructed above, and submit final printed labeling electronically. In addition, please provide the labeling in the Structured Product Labeling (SPL) format. http://www.fda.gov/oc/datacouncil/spl.html

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. 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

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug's labeling with all differences annotated and explained.

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support

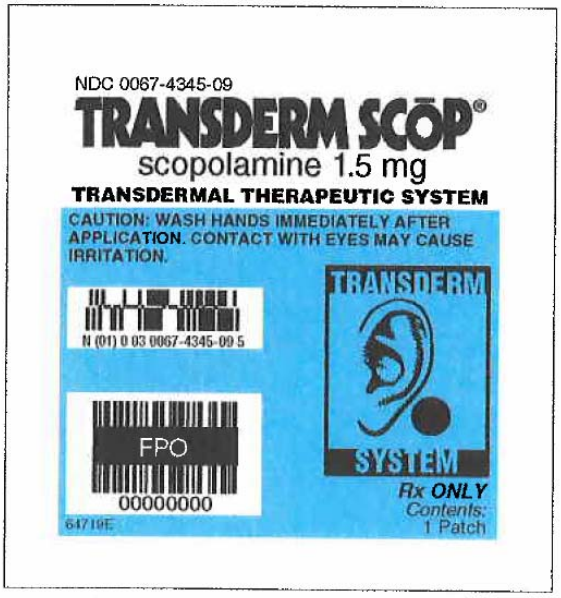
APPEARS THIS WAY ON ORIGINAL

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. MODEL LABELING - This review is based on the labeling of Transderm Scop® of Novartis Consumer Health Inc. (NDA 017874/S-035, approved January 10, 2007). NDA 017874/S-038 is pending review with OND.

front



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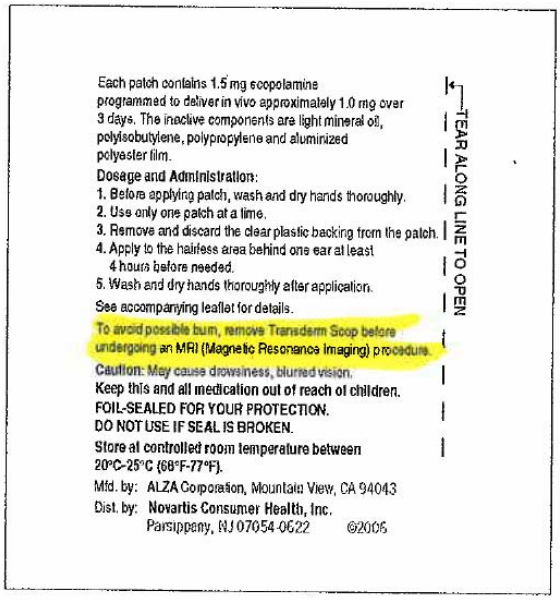

2. USP MONOGRAPH (checked on 1/25/11)
   Transdermal patch is not the subject of USP Monograph.
   PF: Scopolamine Bromide – Packaging and storage: Preserve in tight, light-resistant containers.

3. PATENTS AND EXCLUSIVITIES (checked on 1/25/11)
   There are no unexpired patents or exclusivities.

4. INACTIVE INGREDIENTS:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert **IS** consistent with the listing of inactive ingredients found in the statement of components and composition.

   Contains a backing layer of aluminized,polyester film.

Components and Composition

(b) (4)

[redacted]

5. MANUFACTURING FACILITY
   Manufactured by:
   Aveva Drug Delivery Systems, Inc. (b) (4)
   Miramar, FL 33025

   Manufactured for:
   Perrigo R&D Company
   Allegan, MI 49010

6. PRODUCT DESCRIPTION:
   RLD: tan-colored circular patch, 2.5 cm², on a clear, oversized, hexagonal peel strip.
   ANDA: (b) (4) [redacted] Insert – "tan-colored circular patch, 2.5 cm², on a clear, oversized, (b) (4) peel strip".

7. CONTAINER/CLOSURE SYSTEM:
   Each patch is [redacted] (b) (4)
   (b) (4)

8. PRODUCT LINE:
   RLD: packages of four patches.
   ANDA: packages of four patches.

9. STORAGE CONDITIONS:
   RLD: "The system should be stored at controlled room temperature between 20°C - 25°C (68°F - 77°F)."
   ANDA: "Store at 20°C to 25°C (68°F to 77°F) [see USP controlled room temperature]."

10. DISPENSING RECOMMENDATIONS:
    RLD: Label: "Foil-sealed for your protection. Do not use if seal is broken."
    ANDA: Label: "Foil-sealed for your protection. Do not use if seal is broken."

11. SPL DATA ELEMENTS:
    Not submitted.

12. MEDWATCH: (checked 1/25/11)
    No new alerts or warnings.

13. REMS: (checked 1/25/11)
    No approved REMS.

14. MEDICATION GUIDE: None

15. TALL MAN LETTERS: N/A

16. CITIZEN'S PETITION/SUITABILITY PETITION/PROPRIETARY NAME: None

---

Primary Reviewer: Theresa Liu

Team Leader: Koung Lee

Review – NA 1

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

/s/

THERESA C LIU
01/28/2011

KOUNG U LEE
01/31/2011
For Wm. Peter Rickman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78830

MEDICAL REVIEWS

Addendum to Review of Skin Irritation, Sensitization, and Adhesion Studies Following OSI Inspection Report

ANDA number	078830
Drug Product	Scopolamine Transdermal Extended Release Film
Strength(s)	1 mg/72 hrs
Applicant Name	Perrigo R&D Company
Chemical Name	α -(hydroxymethyl) benzeneacetic acid 9-methyl-3-oxa-9-azatricyclo [3.3.1.$0^{2,4}$] non-7-yl ester
Treatment Indications	Motion Sickness Post Operative Nausea and Vomiting
Reference Listed Drug (RLD)	Transderm Scop® Transdermal Extended Release Film, 1mg/72hr, approved on 12/31/1979
NDA for RLD	017874
RLD Applicant Name	Novartis Consumer Health Inc.
Original Submission Date	02/23/2007
Materials Reviewed	Original submission: 02/23/2007 Resubmission: 3/14/14 (new adhesion study) supporting documents 3 & 15 OSI inspection report: 12/27/2007 (original irritation/sensitization study) DCR original review: 5/17/2013 (not acceptable due to failed adhesion study) FDA final statistical review for a new adhesion study: 11/20/2014 FDA statistical review addendum: 12/23/2014 DCR amendment review: 12/29/2014 (recommended approval)
Primary Reviewer	Sunny Tse, Ph.D. Clinical Reviewer Division of Clinical Review (DCR) Office of Bioequivalence (OBE) Office of Generic Drugs (OGD)
Secondary Reviewer	Carol Y. Kim, Pharm.D. Acting Team Leader, ANDA Team DCR/OBE/OGD
Tertiary Reviewer	Lesley-Anne Furlong, M.D. Acting Director DCR/OBE/OGD
Date of Completion	01/16/2015
DCR Conclusion	The Division of Clinical Review concludes that the skin irritation/sensitization study (study PRG-603) and a new adhesion study (11325301) are adequate to support approval of the application. Based on acceptable history of the clinical site, OSI inspection request for this study was declined.

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Addendum to Review of Skin Irritation, Sensitization, and Adhesion Studies for ANDA 078830 (Amendment)

1 Executive Summary

According to DCR review dated 05/17/2013, irritation and sensitization study (PRG-603) demonstrates that the skin irritation and sensitization potentials of Perrigo's placebo Scopolamine patch, are no worse than those of a positive control (0.1% SLS) of low irritancy. Per Office of Scientific Investigations (OSI) review dated 12/27/2007, the OSI found the clinical data from study PRG-603 acceptable for the Agency's review. [1]

Because adhesion study (PRG-604) failed to demonstrate that the adhesive performance of Perrigo's Scopolamine patch is at least as good as that of the reference listed drug (RLD),[1] the applicant submitted a new adhesion study (11325301) with a larger sample size (N=77). Based on the DCR review dated 01/15/2015, the new adhesion study (11325301) is adequate to demonstrate the adhesive performance of Perrigo's Scopolamine patch is at least as good as that of the RLD, Transderm Scop®.[2] A corresponding OSI inspection for adhesion study 11325301 was requested by DCR dated 09/23/2014 but it was declined.

The OSI declined the DCR's request for a clinical site inspection for the new adhesion study (#11325301) because previously inspected clinical site from (b) (4) was found acceptable for the review. Based on the OSI comments in (b) (4) [3,4] filed under (b) (4) the clinical data from the new adhesion study are acceptable for the review.

The street address (Richmond Avenue versus) for the current clinical site, Novum Pharmaceutical Research Services at Houston Texas, is different (b) (4) (Walnut Bend Lane). However, the OSI concluded that it was acceptable because the location at Walnut Bend Lane is closed and all information was moved to the Richmond Avenue as shown below.

---

[1] http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af802d0569
[2] https://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f88090414e
[3] (b) (4)
[4]

ANDA 078830 Adhesion Study #11325301 clinical investigators/sites	(b) (4)
Robert A. Weaver, M.D., CPI Novum Pharmaceutical Research Services 11300 Richmond Avenue Houston, TX 77082	
Darin B. Brimhall, D.O., FACP, CPI Novum Pharmaceutical Research Services 3760 Pecos McLeod Las Vegas, NV 89121	

Based on overall OSI recommendation for this application, the clinical data from study PRG-603 (irritation/sensitization), and new adhesion study (11325301) are acceptable for the review. The DCR recommends approval based on acceptable irritation/sensitization data and adhesion data.

1.1 Approval Recommendation

The Division of Clinical Review concludes that the new adhesion study 11325301 and previously accepted skin irritation and sensitization study PRG-603 are adequate to support approval of the application. Per OSI comments, the clinical data from new adhesion study 11325301 and skin irritation and sensitization study PRG-603 are acceptable for the review.

1.2 Conclusion and Recommendation

1.2.1 Conclusion

Based on OSI inspection findings from 12/27/2007 and comments from 09/23/2014, clinical data from irritation/sensitization study (PRG-603) and new adhesion study (11325301) are acceptable for the review. Skin irritation and sensitization study PRG-603 demonstrates that the skin irritation and sensitization potentials of Perrigo's placebo Scopolamine patch, are no worse than those of a positive control (0.1% SLS) of low irritancy. The clinical data from a new adhesion study 11325301 presented to ANDA 078830 are adequate to demonstrate that the adhesive performance of Perrigo R&D Company’s Scopolamine Transdermal Extended Release Film, 1 mg/72 hr, is no worse than that of the reference drug product, Transderm Scop®, Transdermal Extended Release Film.

1.2.2 Recommendations

From the DCR perspective, skin irritation/sensitization study (PRG-603) and new adhesion study (11325301) are adequate to support approval of this application.

CLINICAL BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

The Division of Clinical Review has no comment at this time.

APPEARS THIS WAY ON ORIGINAL

Review of Skin Irritation, Sensitization, and Adhesion Studies
AMENDMENT

ANDA number	078830
Drug Product	Scopolamine Transdermal Extended Release Film
Strength(s)	1 mg/72 hrs
Applicant Name	Perrigo R&D Company
Chemical Name	α -(hydroxymethyl) benzeneacetic acid 9-methyl-3-oxa-9-azatricyclo [3.3.1.$0^{2,4}$] non-7-yl ester
Treatment Indications	Motion Sickness Post Operative Nausea and Vomiting
Reference Listed Drug (RLD)	Transderm Scop® Transdermal Extended Release Film, 1mg/72hr, approved on 12/31/1979
NDA for RLD	017874
RLD Applicant Name	Novartis Consumer Health Inc.
Original Submission Date	02/23/2007
Materials Reviewed	Original submission: 02/23/2007 Resubmission : 3/14/14 (new adhesion study) supporting documents 3 & 15 OSI inspection report: 12/27/2007 (original irritation/sensitization study) DCR original review: 5/17/2013 FDA final statistical review pending OSI inspection result for a new adhesion study: 11/20/2014 FDA statistical review addendum: 12/23/2014
Primary Reviewer	Sunny Tse, Ph.D. Clinical Reviewer Division of Clinical Review Office of Generic Drugs
Secondary Reviewer	Carol Y. Kim, Pharm.D. Acting Team Leader, ANDA Team Division of Clinical Review Office of Bioequivalence Office of Generic Drugs
Tertiary Reviewer	Lesley-Anne Furlong, M.D. Acting Director Division of Clinical Review Office of Bioequivalence Office of Generic Drugs
Date of Completion	12/23/2014
DCR Conclusion	The Division of Clinical Review concludes that the new adhesion study (11325301) is adequate to support approval of the application.

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Review of Skin Irritation, Sensitization, and Adhesion Studies for ANDA 078830 (Amendment)

1 Executive Summary

This review focuses on the studies submitted to ensure that the skin irritation and sensitization potentials of the generic product are no greater than those of the reference drug product and that the generic product adheres to the skin as well as the reference drug product over the intended duration of wear.

In the original DCR review of skin irritation/sensitization study (PRG-603) dated 5/17/13, the applicant's product demonstrated non-inferior skin irritation and sensitization potentials against the reference product. The pharmacokinetic study (PRG-604) also demonstrated bioequivalence without use of an overlay after 3 days post application. However, the adhesive performance of the test product evaluated in the pharmacokinetic/adhesion study (PRG-604) was not adequate to demonstrate that the adhesive performance of the test product was at least as good as that of the reference product. In this adhesion study (n=29), the 95% upper confidence bound of the difference between the mean adhesion score for the test minus 1.25 times the reference was above zero (0.1059) although the test mean adhesion score was less than the reference mean adhesion score (0.4711 vs. 0.4944). Neither test nor reference was considered highly adhesive patch (i.e., $\geq$ 90% of patches having $\geq$ 90% adhesion).

Based on the proportion of patch applications with meaningful detachment, defined as $\geq$ 25% detachment (score $\geq$1), the FDA statistical reviewer concluded that the test product might exceed the reference product by at most 14.8 percentage points. For the proportion of patch applications with meaningful detachment, defined as $\geq$50% detachment (score $\geq$2), the FDA statistical reviewer concluded that the test product might exceed the reference product by at most 18.9 percentage points. Since this was a small sample size study (n=29) and the test product was shown to be statistically less adhesive than the reference product, the DCR previously concluded that this study was not sufficient to demonstrate non-inferiority of the test product to the reference product with regard to adhesion performance.

As a result, the applicant provided a new adhesion study with a larger sample size (N=77) in this post Complete Response action submission. The new adhesion study (11325301) compared the adhesion performance of the 1 mg/72 hrs test product with the 1 mg/72 hrs reference product in a multiple-center, single-application, randomized, two-treatment, two period, four-sequence, crossover study. In the protocol, the applicant pre-specified a plan to evaluate the data distribution and use a pre-specified nonparametric method if the data were not normally distributed.

Based on the FDA statistical analysis of adhesion study 11325301 using the statistical method recommended by the draft guidance of this product, the one-sided 95% upper confidence bound for the adjusted mean difference (μ_T -1.25μ_R) is greater than zero (0.068), not within the non-inferiority limit (i.e., T-1.25 R), although the test mean adhesion score was less than the reference mean adhesion score (0.2771 vs. 0.3247). However, due to a higher coefficient of variation (CV $\geq$ 174) observed in this larger sample size study, the upper limit of the one-sided 95% Confidence bound was higher than zero (0) and considered less sensitive for detecting the difference between products. Since the test mean adhesion score was no higher than that of the reference product, no conclusive evidence suggests that the test product is less adhesive.

Based on the proportion of patch applications with meaningful detachment, defined as $\geq$ 25% detachment (score $\geq$1) per mean, the FDA statistical reviewer concluded that the test patch might exceed the reference patch by at most 18.2 percentage points. For the proportion of patch applications with meaningful detachment, defined as $\geq$50% detachment (score $\geq$2) per mean, the FDA statistical reviewer concluded that the test patch might exceed the reference patch by at most 5.4 percentage points. In addition**, in the per-protocol (PP) population, 7 times more reference product had an adhesion score of 4 (patch completely off the skin) than the test product (1 in the test group vs. 7 in the reference group)** based on the frequency of adhesion scores. With regard to the time of detachment, the reference product had a score of 4 (patch completely off the skin) as early as at hour 12 but the test product had a score of 4 as early as at hour 36.

Therefore, the Division of Clinical Review concludes that the adhesion performance of the test product is at least as good as that of the reference product for the following reasons:

1. Based on the mean adhesion scores in the new adhesion study (11325301), no conclusive evidence suggests that the test product is less adhesive to the reference product. The test mean adhesion score is less than the reference mean adhesion score (0.2771 vs. 0.3247).

2. Based on the proportion of patch applications with meaningful detachment evaluated in the new adhesion study (11325301), the proportion of patch application with a meaningful degree of detachment is no higher for the test product than for the reference product and detachment does not occur earlier in the application period for the test product than for the reference product. This is supported as follows:

    a. A significantly higher number of reference product had an adhesion score of 4 (patch completely off the skin) compared to the test product (1 in the test group vs. 7 in the reference group).

    b. For the proportion of patch applications with meaningful detachment, defined as $\geq$50% detachment (score $\geq$2) per mean (i.e., a score of 0 and 1 vs. 2, 3 and 4), the FDA statistical reviewer concluded that the test patch might exceed the reference patch by at most 5.4 percentage points. For the proportion of patch applications

with meaningful detachment, defined as ≥ 25% detachment (score ≥1) per mean (i.e., a score of 0 vs. 1, 2, 3 and 4), the FDA statistical reviewer concluded that the test product might exceed the reference product by at most 18.2 percentage points.

c. With regard to the time of detachment, the reference product had a score of 4 (patch completely off the skin) as early as at hour 12 but the test product had a score of 4 as early as at hour 48

3. To support approval of this product based on adhesion assessment, the test product must show no clinically meaningful difference with regard to degree of detachment in addition to the mean adhesion scores.

4. Based on the applicant's pre-specified a non-parametric analysis to compare the median of the test product versus the reference product using the bootstrap methods, the applicant demonstrated that the test product was shown to be non-inferior to the reference product. It is questionable whether this statistical method is appropriate for evaluating adhesion performance between products because the median of adhesion scores would be most likely be zero in a bootstrap sample. The FDA statistical reviewer is concerned that this approach may loosen the current criterion for evaluating the adhesion performance.

5. The original PK study (PRG-604) was adequate to demonstrate bioequivalence between the test and reference products but this study was underpowered to meet the adhesion non-inferiority limit. As no overlay (tape) was used to improve adhesion, the fact that the test product demonstrated bioequivalence over a three-day wear period provides strong supportive evidence that any differences in adhesion between test and reference products were clinically insignificant.

Based on the above stated reasons, DCR recommends the approval regulatory action for this ANDA.

1.1 Approval Recommendation

The Division of Clinical Review concludes that the new adhesion study (11325301) is adequate to support approval of the application.

1.2 Summary of Clinical Findings (new adhesion study 11325301)

1.2.1 Brief Overview of Clinical Program

Study Design	This was a multiple-center, single-application, randomized, two-treatment, two period, four-sequence, crossover study comparing the adhesive properties of the test patch relative to those of the reference patch. • One (1) scopolamine transdermal therapeutic system (1 mg/72 hours) was applied behind the ear (postauricular area) and kept in place for

	approximately 72 hours in each period of the study. • Subjects arrived at the clinic before patch application in each study period and returned to the clinical facility at 12, 24, 36, 48, 60, and 72 hours after patch application for adhesion assessments. All procedures were performed on outpatient basis, such that the study reflected the patch use in clinical practice. Patch size: Test product: 2.5 cm^2 (1 mg/72 hours); containing 1.3 mg active ingredient Reference product: 2.5 cm^2 (1 mg/72 hours); containing 1.5 mg active ingredient ***Reviewer's Comment:*** *The same drug content is released for the test and reference products.*
Study Randomization	80 healthy adult subjects were enrolled.

1.2.2 Comparative Adhesion

The adhesion data from the study 11325301 are adequate to demonstrate that the test product is no worse than that of the reference product with regard to the adhesion performance. See Review of Statistical Report in section 2.6.2 below for details.

1.2.3 Comparative Safety

Overall clinically Significance between products	none
Total adverse events reported	60 adverse events were reported by 38 of the 80 subjects who participated in this study.
Total number of subjects discontinued due to adverse events	none
Application site related adverse events	The incidence of application site pruritus for the test (8.97%) was comparable to the reference (8.86%). Test: n=7, Application site pruritus Reference: n=7, Application site pruritus
Most frequently reported adverse events	Application site pruritus: test n=7, reference n=7
Most frequently reported treatment related adverse events	Blurred vision: test n=7, reference n=4 Dry mouth: test n=6, reference n=5
Death	none
Serious adverse events	none
Clinically significant laboratory findings	Subject (b) (6) exhibited increased aspartate aminotransferase and increased alanine aminotransferase that were determined to be significantly different from the screening results. This

	subject was contacted to schedule repeat analysis but was unable to return to the clinical facility. The lab sample was taken 7 minutes after period II (test product) patch removal. Subject (b) (6) exhibited increased blood glucose that was determined to be clinically significant. This subject was contacted to schedule repeat analysis but did not return to the clinical facility. The lab sample was taken 10 minutes after period II (reference product) patch removal. ***Reviewer's Comment:*** *These laboratory findings for subjects (b) (6) are not likely to affect the study outcome.*

2 Clinical Review

2.1 Introduction and Background

2.1.1 Summary of Drug Information

Reference Listed Drug	Transderm Scop® Transdermal Extended Release Film, 1mg/72hr
RLD Applicant name	Novartis Consumer Health Inc.
NDA #	017874
Date of RLD Approval	12/31/1979
Approved Indications	Motion Sickness Post Operative Nausea and Vomiting
Recommended Dosing Regimens/dosing considerations	DO NOT cut the patch. Apply ONE patch in the postauricular area to prevent: Motion Sickness • Apply 4 hrs before antiemetic effect is required- for use up to 3 days • For use longer than 3 days, remove current patch and place new patch behind other ear Post Operative Nausea and Vomiting • Apply evening before scheduled surgery • For cesarean section, apply 1 hour prior to surgery • Discard 24 hrs after surgery
Recommended application site	postauricular area

Absorption	• Scopolamine is well absorbed percutaneously. • Following application to the skin behind the ear, circulating plasma levels are detected within 4 hours with peak levels being obtained, on average, within 24 hours. • The average plasma concentration produced is 87 pg/mL (0.28 nM) for free scopolamine and 354 pg/mL for total scopolamine (free + conjugates).
Mechanism of Action	• Scopolamine, a belladonna alkaloid, is an anticholinergic agent. • Scopolamine acts: i) as a competitive inhibitor at postganglionic muscarinic receptor sites of the parasympathetic nervous system, and ii) on smooth muscles that respond to acetylcholine but lack cholinergic innervation. • It has been suggested that scopolamine acts in the central nervous system (CNS) by blocking cholinergic transmission from the vestibular nuclei to higher centers in the CNS and from the reticular formation to the vomiting center. • Scopolamine can inhibit the secretion of saliva and sweat, decrease gastrointestinal secretions and motility, cause drowsiness, dilate the pupils, increase heart rate, and depress motor function.
Boxed Warnings	none
Use in specific populations	• Pregnancy: Based on animal data, may cause fetal harm • Nursing mothers: Caution should be exercised when administered to a nursing woman

Warnings and Precautions	• Use with caution in patients with open angle glaucoma • Stop use if patient experiences symptoms of angle closure glaucoma • Can cause temporary dilation and blurred vision if scopolamine contacts the eyes • Use caution in patients with a history of seizures or psychosis • Use with caution in patients with pyloric obstruction, urinary bladder neck obstruction, or patients suspected of having intestinal obstruction • Stop use if patient has difficulty urinating • Idiosyncratic reactions, such as confusion, agitation, speech disorder, hallucinations, paranoia and delusions, may occur with therapeutic doses of scopolamine • A safe and effective dose has not been established in the pediatric population • Use with caution in the elderly because of the increased likelihood of CNS effects, such as hallucinations, confusion and dizziness • Should be used with caution in patients with impaired renal or hepatic function because of the increased likelihood of CNS effects • May cause drowsiness or disorienting effects, therefore patients should be cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery • Skin burns have been reported in patients undergoing MRI testing
Commonly reported Adverse Events (e.g., ≥ 2%)	Most commonly reported adverse reactions in treatment of motion sickness clinical trials are dry mouth, drowsiness and blurred vision. Most common adverse reactions during post operative nausea and vomiting trials[1] (≥ than 3%) are dry mouth (28.9%), dizziness (12.4%), somnolence (7.8%), urinary retention (7.2%), agitation (6.1%), visual impairment (5.0%), confusion (3.9%), mydriasis (3.5%), and pharyngitis (3.3%).

[1] NDA 017874 04/30/2013 Labeling Revision page 5/17

2.1.2 Regulatory Background

Guidance	Scopolamine Film, Extended Release/Transdermal http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM179189.pdf
Guidance post date	Finalized on October 2011
Adhesion study recommendations	• Adhesion performance of the intact test product and RLD patches must be formally evaluated and compared in the PK bioequivalence study or in a separate parallel or crossover adhesion study of single 72-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. • 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.

2.1.3 Other Relevant Information

none

2.2 Description of Clinical Data and Sources

	Adhesion Study
Protocol Number/Study Number	11325301
Study Title	A Study to Evaluate the Relative Adhesive Properties of a Test Scopolamine Transdermal Therapeutic System, 1.31 mg (Manufactured by AVĒVA Drug Delivery Systems, an Apotex Company; Distributed by Perrigo) Compared to TRANSDERM-SCŌP® (Scopolamine) Transdermal Therapeutic System, 1.5 mg (Manufactured by ALZA Corporation; Distributed by Novartis Consumer Health, Inc.) in Healthy Adult Subjects
CRO	Novum Pharmaceutical Research Services
Study Period	10/21/2013 to 11/17/2013
Study Centers/address	Site No. 01 There was no clinical site designated as Site No. 01 for this study.[2]

[2] The applicant used sites no. 2 and 3 only

	Site No. 02 Novum Pharmaceutical Research Services 11300 Richmond Avenue Houston, TX 77082 United States of America (USA) 40 subjects enrolled Site No. 03 Novum Pharmaceutical Research Services 3760 Pecos McLeod Las Vegas, NV 89121 United States of America (USA) 40 subjects enrolled
Principal Investigators	Site No. 02 Robert A. Weaver, M.D., CPI Site No. 03 Darin B. Brimhall, D.O., FACP, CPI
No. subjects enrolled	80

2.3 Clinical Review Methods

2.3.1 Overview of Materials Consulted in Review

Original Submission	02/23/2007 (0000): MDS Pharma Services • Project AA31201; Protocol No. PRG-603 (skin irritation/sensitization study): DCR found this study acceptable. • Protocol No. PRG-604 (adhesion study): DCR found this study **unacceptable**.
Study Amendments for adhesion study	03/14/2014 (0012): The applicant submitted a new adhesion study (11325301) to show non-inferiority of the test product to the RLD with regard to adhesion performance.
FDA Statistical Review	20-Nov-2014 23-Dec-2014 (addendum)

2.3.2 Overview of Methods Used to Evaluate Data Quality and Integrity

OSI inspection requested date	09/23/2014 (for the new adhesion study)
Office of Scientific Investigations (OSI) Report Date	Pending at this time.
OSI inspection findings:	Pending at this time.

2.3.3 Were Trials Conducted in Accordance with Accepted Ethical Standards

	Adhesion Study
Protocol Number/Study Number	11325301
Ethical Standards acceptable?	**Yes** \\cdsesub1\evsprod\anda078830\0012\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\11325301\report-body.pdf page 10/56

Reviewer's Comment: *The study appears to be in compliance with accepted ethical standards.*

2.3.4 Evaluation of Financial Disclosure

	Adhesion Study
Protocol Number/Study Number	11325301
Financial Disclosure Form 3454	Financial Disclosure Form 3454 was not given by the applicant. Investigators supplied statements that were consistent with Form 3454 expiration date December 31, 2015 statement #1. \\cdsesub1\evsprod\anda078830\0012\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\11325301\investigator-list.pdf [page 24/156]

2.4 Review of Adhesion Study

2.4.1 Brief Statement of Conclusions

Per FDA statistical analysis dated 20-Nov-2014, the new adhesion study (11325301) does not demonstrate that adhesion performance of the test product is no worse than that of the reference product.

The addendum to the statistical analysis dated 23-Dec-2014 examines the test and reference adhesion data the applicant's use of nonparametric statistical methods. DCR concluded that the new adhesion study (11325301) data were adequate to support approval.

2.4.2 General Approach to Review of the Skin Adhesion Performance of the Drug

The applicant's data were evaluated using the criteria set forth in the OGD Guidance for this product. The mean cumulative adhesion scores were analyzed using a mixed linear model. The one-sided 95% upper confidence bound for the adjusted mean difference (μ_T -1.25$_{\mu R}$) was estimated to determine if adhesion performance of the test product was no worse than that of the reference product.

2.4.3 Detailed Review of Skin Adhesion Study (Study 11325301)

2.4.3.1 Protocol

Applicant's protocol #:	PRG-NY-14-007
Title	A Study to Evaluate the Relative Adhesive Properties of a Test Scopolamine Transdermal Therapeutic System, 1.5 mg (Perrigo Research & Development Co.) Compared to TRANSDERM-SCOP® (Scopolamine) Transdermal Therapeutic System, 1.5 mg (Novartis) in Healthy Adult Subjects
Objectives	The objective of this study was to compare the adhesive properties of a test formulation of Test scopolamine transdermal therapeutic system, 1.31 mg (manufactured by AVĒVA Drug Delivery Systems, an Apotex Company; distributed by Perrigo) relative to those of the marketed reference formulation, TRANSDERM-SCŌP® (scopolamine) transdermal therapeutic system, 1.5 mg (manufactured by ALZA Corporation; distributed by Novartis Consumer Health, Inc.), in healthy adult subjects.
Original Protocol Date (s)	10/01/13
IRB approval Date(s)	Protocol Rev. 0 : 10/01/13 (adhesion study) Consent Form Rev. 0: 10/01/13 (adhesion study)
Protocol Amendment(s)	PRG-NY-14-007 (Revision 1) – 10/03/13; The following revision was made to the protocol dated 10/01/13: Principal Investigator for the Houston, TX site was changed (b) (4) (b) (4) to Robert A. Weaver, M.D., CPI

Reviewer's Comment: *There were no changes to the protocol after the study initiated.*

2.4.3.1.1 Study Design (per applicant)

Overall Study Design and Plan

Procedures and Observations

Procedure	Screen[1] Day -28 → Day -1	Period I			Period II			
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 3	Day 7
Informed Consent	X							
Medical History	X							
Physical Examination	X							
Clinical Laboratory Tests	X							X
Tonometry Test	X							
Clinic Visit	X	X	X	X	X	X	X	X
Vital Signs[2]	X	X	X	X	X	X	X	X
Urine/Saliva Drug Test[3]	X	X			X			
Urine Pregnancy Test[4]	X	X			X			
Patch Application[5]		X			X			
Patch Adhesion Assessment[6]		X	X	X	X	X	X	X
Patch Removal[7]					X			X
Monitor and/or Record Adverse Events and Concomitant Medications		X	X	X	X	X	X	X

[1]Within 28 days of the first application (Day 1).

[2]Vital Signs (temperature, respiratory rate, pulse rate, and blood pressure) were measured before patch application in Period I. Blood pressure and pulse rate were measured approximately 24, and 48 hours (±60 minutes) after the patch has been applied in each period, before patch application in Period II, and at the end of the study (or early termination).

[3]Subjects tested for alcohol, THC, and cocaine metabolites. Results must be negative before patch was applied to the subject.

[4]For all female subjects, regardless of child-bearing potential. Results must be negative before patch was applied to the subject.

[5]Dose (1 x test or 1 x reference scopolamine transdermal system) applied the morning of Day 1 (Period I dosing) and the morning of Day 4 (Period II dosing). Patch application in Period II occurred immediately following the patch removal in Period I.

[6]Adhesion assessments conducted immediately after application (0 hour) and at 12, 24, 36, 48, 60, and 72 hours (before patch removal) after application (± 60 minutes) in each Period.

[7]Patches were removed 72 hours after application in each Period.

Assessments	Description
Scale for evaluation of adhesion score	0 = ≥ 90% adhered (essentially no lift off the skin) 1 = ≥ 75% to < 90% adhered (some edges only lifting off the skin) 2 = ≥ 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) No overlays, adhesive tape, or similar products were applied during the application period.

Blinding	Not applicable
Randomization	One test and one reference patch (A or B) were randomized by study period and ear (Right or Left). The randomization was generated in blocks of 4 with each sequence appearing once in each block. The sequence scheme is shown below:
Retention of Reserve Samples	OSI inspection is still pending to confirm it.

Sequence	Period I	Period II
1	Left A	Right B
2	Left B	Right A
3	Right A	Left B
4	Right B	Left A

Treatments:

Table 1: Treatment Arms

Product	Test	Reference
Treatment ID	Test A	Reference B
Product Name	Scopolamine Transdermal System 1.31 mg/unit	Transderm Scop® (scopolamine) 1.5 mg/unit
Manufacturer	Aveva Drug Delivery Systems [redacted] (b) (4) manufacturer for Perrigo)	Manufactured by ALZA Corporation Distributed by Novartis Consumer Health, Inc.
Batch/Lot No.	41719	1206594/ 130538
Manufacture Date	08/27/13	N/A
Expiration Date	N/A	JUL/15

Strength	1.31 mg /unit	1.5 mg /unit
Dosage Form	Transdermal patch	Transdermal patch
Dose Administered	1 patch	1 patch
Route of Administration	Transdermal	Transdermal
Dosing regimen	1 patch is applied for 72 hrs	1 patch is applied for 72 hrs
Patch size	2.5 cm^2	2.5 cm^2

Reviewer's Comment: *Treatment application site, frequency of application, and study duration were consistent with the recommendation in the approved labeling of the RLD and the guidance recommendation. For the test and reference products, the same drug content is released.*

Study Population:

Inclusion Criteria	1. Males and females, 18 years of age or older. 2. Females subjects of childbearing potential must be prepared to either abstain from sexual intercourse or use a reliable barrier method of contraception (e.g. condom with spermicide, diaphragm, IUD, contraceptive sponge) for at least 14 days before and throughout the duration of study or have used a hormonal method of contraception for at least 30 days before the study and will continue to use the same type of hormonal contraceptive during the study. 3. Good health as determined by lack of clinically significant abnormalities in health assessments performed at screening. 4. Signed and dated informed consent form, which meets all criteria of current FDA regulations. 5. Able and willing to meet the visit requirements of the study.
Exclusion Criteria	1. Females who are pregnant, lactating or likely to become pregnant during the study. 2. History of allergy or sensitivity to scopolamine, other belladonna alkaloids or other ingredients in the patches, including glues/adhesives, or history of any drug hypersensitivity or intolerance which, in the opinion of the Investigator, would compromise the safety of the subject or the study. 3. Significant history or current evidence of chronic infectious disease, system disorder, or organ dysfunction, especially hypertension, hepatic or renal disorders. 4. Significant history or current evidence of glaucoma or elevated intraocular pressure. 5. History or current evidence of pyloric obstruction, urinary bladder neck obstruction, or intestinal obstruction. 6. Any history of seizures or psychosis, or other central nervous system (CNS) diseases that may be aggravated by scopolamine use. 7. Anticipate having a Magnetic Resonance Imaging (MRI) scan performed during the study

	8. Presence of any skin condition such as scratches, cuts, scars, abrasions, excessive hair, tattoos, moles, recently shaved skin, uneven skin texture, or excessively oily skin at the application areas that may affect the application of the study patch or the adhesive properties of the patch. 9. History of psychiatric disorders occurring within the last two years that required hospitalization or medication. 10. Presence of a medical condition requiring regular treatment with prescription drugs that could possibly interact with the study drug as determined by the Investigator. 11. Receipt of any drug as part of a research study within 30 days before the patch application. 12. Drug or alcohol addiction requiring treatment in the past 12 months. 13. History of excessive alcohol consumption (on average more than 14 units of alcohol/week) during the past 12 months. 14. Positive test results for alcohol, marijuana, and cocaine metabolites screening. 15. Positive urine pregnancy test at screening.

Reviewer's Comment: *The applicant's inclusion criterion #1 did not have an age range as recommended in the guidance of this product (i.e., 18-65 years) but the study included subjects with an age range between 20-64 years. This is acceptable.*

The applicant's inclusion criteria #2-5 and exclusion criteria #1-15 are acceptable.

Criteria for removal from the study	Subjects were advised that they were free to withdraw from the study at any time for any reason or, if necessary, the Investigator or Sponsor could withdraw a subject from the study to protect the health of a subject. A subject could also be withdrawn for not complying with study procedures. If the patch completely detached within the 72-hour period of application in Period I, the subject was to continue in Period II of the study. In Period II, if the patch completely detached, the subject was to be discontinued from the study after completing the applicable end of study procedures. Subjects who dropped out of the study were not replaced.
Prior and concomitant therapy	The subjects were questioned about their use of any prescription and over the counter (OTC) medications including vitamin and herbal products and nutritional supplements at screening and check-in. Subjects that were on a stable regimen of medications that are not contraindicated to be taken with scopolamine, that the Investigator did not believe would affect subject safety or the integrity of the study data, were allowed in this study.
Treatment compliance	• Application of the patches was performed by members of the

	study staff under the supervision of the Investigator. • Subjects were not permitted to apply make-up, creams, lotions, powders, or other topical products to the application site for at least 24 hours before initial application until the end of the study, as this could affect the adhesive performance. • The site of application could not have been recently shaved. All subjects reported compliance with these restrictions. • Subjects were instructed to avoid hot-tubs, swimming, excessive soaking or wetting of the patches during the patch application period. Considering production of sweat might affect patch adherence, subjects were also instructed to avoid steam baths or saunas, and vigorous exertion. • Subjects were also instructed to avoid rubbing, pulling, scratching, or touching the patches or other activities that might cause the patch to become displaced. Subjects were instructed not to try to reapply or press the patch back into place should it come loose. If a patch completely detached, subjects were instructed to note the date and time of complete patch detachment. • No overlays, tapes, labels, or similar re-enforcements were applied to the patches to hold them in place.
Assessment of rating compliance	• All patches were applied by the clinical staff. • Immediately after application (0 hour) and at 12, 24, 36, 48, 60, and 72 hours (before patch removal) after application (±60 minutes), the adhesion of the patch application was evaluated by a trained scorer.

Reviewer's Comment: *The per protocol population for adhesion analysis should include subjects with no issues of compliance for the adhesion assessment. Seventy seven of eighty enrolled subjects were included in the FDA and applicant's PP populations. Three subjects were excluded from the FDA and applicant's PP populations due to significant protocol violations.*

2.4.3.1.2 Endpoints/Variables (per applicant)

Adhesion Evaluation	The primary endpoint of adhesion is the Cumulative Adhesion Score (CAS) during the 72-hour application period (i.e. the CAS for a specific subject and patch type is the sum of the adhesion scores recorded immediately after the patch has been applied (0 hour) + 12 + 24 + 36 + 48 + 60 + 72 hours after application). Descriptive statistics (e.g. mean, standard deviation, median, minimum, and maximum) is also generated on CAS. The primary objective related to adhesion is whether the level of adhesion of the test patch is no worse than (non-inferior to) that of the reference patch. Because the adhesion scale shows better adhesion for lower values, the relevant hypotheses for evaluating non-inferiority are: H_0: T - (1.25 x R) > 0 (not non-inferior)

	H_1: T - (1.25 x R) ≤ 0 (non-inferior) Statistical analysis was to be performed to compare the adhesive properties of the test patch to those of the reference patch.

Reviewer's Comment: *The study design was consistent with the general guidance recommended for this product.*

2.4.3.1.3 Statistical analysis plan (per applicant)

Analysis Subject Populations	Safety Population: The safety population included all subjects who have at least one patch applied. Adhesion Analysis Population: • ITTA: Intent to Treat Population for Adhesion • PPPA: The PPPA included patches from all subjects who complete the study with no protocol deviations or issues of non-compliance that may compromise the integrity of the study outcome, adhesive properties of the patch, or adhesion assessment.
Adhesion Analysis Population	The Per Protocol Population for Adhesion (PPPA) was used for the non-inferiority analysis.
Non-inferiority statistical analysis plan (e.g. Missing values or dropouts, sample size etc.)	See FDA statistical review dated 20-Nov-2014 and addendum dated 23-Dec-2014 for details.
Safety assessment	Safety was evaluated by the collection of adverse events.

Reviewer's Comment: *No changes to the study conduct or measurements were implemented after the initiation of the study.*

2.4.3.2 Results (Per applicant)

Adhesion Study (#11325301)

Subject Disposition

Table 2: Number of Subjects in the Applicant's ITT and PP Populations

	Test	Reference
Randomized	**80**	**80**
Total ITT population for Adhesion	**80**	**80**
Total PP population for Adhesion	**77**	**77**
Total Exclusion from PP population	3	3
Reason for exclusion from PP		
Subject did not complete the study	2	2
Patch Detachment due to manual detachment, subject safety, excessive irritation or withdrew consent	1	1

Demographics

Subjects Included in the ITTA (N=78 for Test A, N=79 for Reference B)

	Test A	Reference B
Gender		
Male	38 (48.72%)	40 (50.63%)
Female	40 (51.28%)	39 (49.37%)
Ethnicity		
Hispanic/Latino	24 (30.77%)	24 (30.38%)
Not Hispanic/Latino	54 (69.23%)	55 (69.62%)
Race		
American Indian or Alaska Native	1 (1.28%)	1 (1.27%)
Asian	0 (0.00%)	0 (0.00%)
Black or African American	37 (47.44%)	38 (48.10%)
Native Hawaiian or Other Pacific Islander	0 (0.00%)	0 (0.00%)
White	23 (29.49%)	23 (29.11%)
Other	17 (21.79%)	17 (21.52%)
Age (yrs)		
Mean ± SD	41.2 ±11.4	41.5 ± 11.3
Median	44.5	45.0
Minimum	20	20
Maximum	64	64
Age Groups		
< 18	0 (0.00%)	0 (0.00%)
18 - 40	32 (41.03%)	32 (40.51%)
41 - 64	46 (58.97%)	47 (59.49%)
65 - 75	0 (0.00%)	0 (0.00%)
> 75	0 (0.00%)	0 (0.00%)

Subjects Included in the PPPA (N=77)

Gender	
Male	38 (49.35%)
Female	39 (50.65%)
Ethnicity	
Hispanic/Latino	24 (31.17%)
Not Hispanic/Latino	53 (68.83%)
Race	
American Indian or Alaska Native	1 (1.30%)
Asian	0 (0.00%)
Black or African American	36 (46.75%)
Native Hawaiian or Other Pacific Islander	0 (0.00%)
White	23 (29.87%)
Other	17 (22.08%)
Age (yrs)	
Mean ± SD	41.4 ±11.3
Median	45.0
Minimum	20
Maximum	64
Age Groups	
< 18	0 (0.00%)
18 - 40	31 (40.26%)
41 - 64	46 (59.74%)
65 - 75	0 (0.00%)
> 75	0 (0.00%)

Reviewer's Comment: *Each subject received both the test and the reference patches.*

Protocol Deviations/violations:

Site No.	Subject No.	Subject Initials	Protocol Deviation Summary	Included in PPPA
02		(b) (6)	Consumption/ use of a restricted item: Reasons other than indication	No

The protocol specified that subjects who were on a stable regimen of medications that are not contraindicated to be taken with scopolamine, that the investigator did not believe would affect subject safety or the integrity of the study data, were allowed in this study. Subject (b) (6) reported taking dextroamphetamine sulfate, 30 mg, once, for recreational purposes on Day 3 while the Period I patch was applied. This medication use was reported to clinical staff at the Day 4 visit when the Period I patch was removed as scheduled. Because the subject was not considered to be on a stable regimen, the investigator discontinued this subject from further study participation when this medication use was reported. Thus, this subject did not receive a Period II patch application. The subject had no symptoms and reported no adverse events; therefore, his safety was not affected. Because this deviation did not affect the integrity of the study data, this subject's data were included in the safety and ITTA analyses only.

Reviewer's Comment: *This reviewer agrees with the investigator's decision for the removal of subject* (b) (6) *from the study.*

Adhesion Score Tables and Analysis from the Applicant's Submission[3]

Table 3: Primary Efficacy Analysis of Mean Cumulative Adhesion Scores: [Study #11325301] (per Applicant)

Table 11.4.1.1 Cumulative Adhesion Scores (CAS) (sum of the adhesion scores at 0, 12, 24, 36, 48, 60 and 72 hours)

	Product*	N	Mean	SD	Min.	Median	Max.
CAS	A	77	1.66	2.90	0.00	0.00	13.00
	B	77	1.95	4.65	0.00	0.00	24.00

*A = Scopolamine Transdermal Delivery System, 2.5 cm^2, label claim 1.31 mg/unit (Manufactured by AVĒVA Drug Delivery Systems, an Apotex Company; Distributed by Perrigo)

B = TRANSDERM-SCŌP® (scopolamine) transdermal system, 1.5 mg (Manufactured by ALZA Corporation; Distributed by Novartis Consumer Health, Inc.)

Table 11.4.1.4 Statistical Results of Adhesion Analysis for PPPA (N=77) Using PROC MIXED

Variable	Hypotheses	Test Statistic $\mu_T - 1.25*\mu_R$	Upper Bound of One-Sided 95% Confidence Interval†
CAS	H_0: $\mu_T - 1.25*\mu_R > 0$ H_1: $\mu_T - 1.25*\mu_R \leq 0$	-0.7930	0.2977

†If Upper bound of the CI is ≤ 0 then adhesion of test product is non-inferior to that of the reference product.

The upper bound for the 95% one-sided confidence interval was not less than zero (0); however, as the individual CAS are highly skewed and non-normally distributed, the analysis of relative differences between test and reference scores using parametric methods is 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.

[3] Tables are taken from supporting document 15 study report at \\cdsesub1\evsprod\anda078830\0012\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\11325301\report-body.pdf

Table 11.4.1.2 Summary of 90% two-sided (95% one-sided) Bootstrap Confidence Interval for the Expected Median Difference (T - 1.25*R) in Cumulative Adhesion Scores (N=77)

No. of Bootstrap Simulations	Estimate	Expected Treatment Difference for Adhesion Score	Lower Bound of One-Sided 95% Confidence Interval	Upper Bound of One-Sided 95% Confidence Interval†
10,000	T - 1.25*R	0	0	0

†If the upper bound of the CI is ≤ 0 then the adhesion of the test product is non-inferior to that of the reference product.

The upper bound for the 95% one-sided confidence interval was equal to zero (0). Therefore, the adhesion of the test patch was considered to be non-inferior to that of the reference patch.

Table 4: Frequency of Adhesion Scores: [Study #11325301] (per Applicant)

Table 11.4.1.5 A Frequency of Adhesion Scores for Test Patch A* for PPPA (N = 77)

	Adhesion Score				
Hour	0 N (%)	1 N (%)	2 N (%)	3 N (%)	4 N (%)
0	77 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
12	73 (94.81)	4 (5.19)	0 (0.00)	0 (0.00)	0 (0.00)
24	68 (88.31)	9 (11.69)	0 (0.00)	0 (0.00)	0 (0.00)
36	59 (76.62)	17 (22.08)	1 (1.30)	0 (0.00)	0 (0.00)
48	55 (71.43)	17 (22.08)	4 (5.19)	0 (0.00)	1 (1.30)
60	54 (70.13)	18 (23.38)	3 (3.90)	1 (1.30)	1 (1.30)
72	52 (67.53)	18 (23.38)	4 (5.19)	2 (2.60)	1 (1.30)

*A = Scopolamine Transdermal Delivery System, 2.5 cm^2, label claim 1.31 mg/unit (Manufactured by AVĒVA Drug Delivery Systems, an Apotex Company; Distributed by Perrigo)

Table 11.4.1.5 B Frequency of Adhesion Scores for Reference Patch B* for PPPA (N = 77)

	Adhesion Score				
Hour	0 N (%)	1 N (%)	2 N (%)	3 N (%)	4 N (%)
0	77 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
12	76 (98.70)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.30)
24	71 (92.21)	4 (5.19)	0 (0.00)	0 (0.00)	2 (2.60)
36	68 (88.31)	5 (6.49)	0 (0.00)	0 (0.00)	4 (5.19)
48	64 (83.12)	7 (9.09)	1 (1.30)	0 (0.00)	5 (6.49)
60	59 (76.62)	9 (11.69)	2 (2.60)	0 (0.00)	7 (9.09)
72	57 (74.03)	11 (14.29)	2 (2.60)	0 (0.00)	7 (9.09)

*B = TRANSDERM-SCŌP® (scopolamine) transdermal system, 1.5 mg (Manufactured by ALZA Corporation; Distributed by Novartis Consumer Health, Inc.)

Table 11.4.1.7 A Frequency of Adhesion Scores for Test Patch A* for ITTA (N = 78)

	Adhesion Score				
Hour	0 N (%)	1 N (%)	2 N (%)	3 N (%)	4 N (%)
0	78 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
12	74 (94.87)	4 (5.13)	0 (0.00)	0 (0.00)	0 (0.00)
24	69 (88.46)	9 (11.54)	0 (0.00)	0 (0.00)	0 (0.00)
36	59 (75.64)	18 (23.08)	1 (1.28)	0 (0.00)	0 (0.00)
48	55 (70.51)	18 (23.08)	4 (5.13)	0 (0.00)	1 (1.28)
60	54 (69.23)	19 (24.36)	3 (3.85)	1 (1.28)	1 (1.28)
72	52 (67.53)	18 (23.38)	4 (5.19)	2 (2.60)	1 (1.30)

*A = Scopolamine Transdermal Delivery System, 2.5 cm^2, label claim 1.31 mg/unit (Manufactured by AVĒVA Drug Delivery Systems, an Apotex Company; Distributed by Perrigo)

Table 11.4.1.7 B Frequency of Adhesion Scores for Reference Patch B* for ITTA (N = 79)

	Adhesion Score				
Hour	0 N (%)	1 N (%)	2 N (%)	3 N (%)	4 N (%)
0	79 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
12	78 (98.73)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.27)
24	73 (92.41)	4 (5.06)	0 (0.00)	0 (0.00)	2 (2.53)
36	69 (87.34)	5 (6.33)	1 (1.27)	0 (0.00)	4 (5.06)
48	65 (82.28)	7 (8.86)	1 (1.27)	0 (0.00)	6 (7.59)
60	60 (75.95)	9 (11.39)	2 (2.53)	0 (0.00)	8 (10.13)
72	58 (73.42)	11 (13.92)	2 (2.53)	0 (0.00)	8 (10.13)

*B = TRANSDERM-SCŌP® (scopolamine) transdermal system, 1.5 mg (Manufactured by ALZA Corporation; Distributed by Novartis Consumer Health, Inc.)

Reviewer's Comments:

For reference, please see statistical review addendum Frequency tables for comparison of frequency of adhesion scores between test and reference products for the original and additional adhesion study.

https://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f8808e6259 (pages 4-6)

This reviewer does not recommend any further subject adjustment for the FDA adhesion analysis.

2.4.4 Comparative Study Conclusion

Parameters	Conclusion
Adhesion Performance (Study #11325301)	The adhesion performance of the test product is shown to be at least as good as that of the reference product based upon the proportion of test versus reference patch applications with no meaningful degree of detachment over a 72 hour period.

2.5 Comparative Review of Safety

2.5.1 Brief Statement of Conclusions

The study showed no clinically significant difference between generic and reference products with regard to application site related adverse events.

2.5.2 Description of Adverse Events (per applicant)

Sixty (60) adverse events were reported by 38 of the 80 subjects who participated in this study. There were no serious adverse events. Fifty-nine (59) adverse events were treatment-emergent events, of which thirty (30) occurred after administration of the test product, and twenty-nine (29) occurred after administration of the reference product. One (1) adverse event of dry mouth began about 2 hours before the initial application of patches in Period I but was not reported by the subject until Day 3 and continued throughout the duration of the study. The Investigator assessed the subject's condition when this adverse event was reported and approved the subject's continued participation in the study.

All sixty (60) adverse events were considered "mild", fifty-eight (58) resolved spontaneously and two (2) had not resolved by the end of the study. The most frequently reported adverse events were dry mouth (12 subjects), application site pruritus (12 subjects), and blurred vision (10 subjects).

No patches were removed during the study due to a significant irritation reactions.

Body System/Adverse Event	Test A N (%)	Reference B N (%)	Overall* N (%)
Eye disorders			
Blepharospasm	0 (0.00%)	1 (1.27%)	1 (1.25%)
Dry eye	0 (0.00%)	1 (1.27%)	1 (1.25%)
Vision blurred	7 (8.97%)	4 (5.06%)	10 (12.50%)
Gastrointestinal disorders			
Diarrhoea	0 (0.00%)	1 (1.27%)	1 (1.25%)
Dry mouth	6 (7.69%)	5 (6.33%)	12 (15.00%)*
Nausea	1 (1.28%)	1 (1.27%)	2 (2.50%)
General disorders and administration site conditions			
Application site pruritus	7 (8.97%)	7 (8.86%)	12 (15.00%)
Fatigue	1 (1.28%)	0 (0.00%)	1 (1.25%)
Investigations			
Alanine aminotransferase increased	1 (1.28%)	1 (1.27%)	2 (2.50%)
Aspartate aminotransferase increased	0 (0.00%)	1 (1.27%)	1 (1.25%)
Blood glucose increased	0 (0.00%)	1 (1.27%)	1 (1.25%)
Heart rate decreased	0 (0.00%)	1 (1.27%)	1 (1.25%)
Liver function test abnormal	1 (1.28%)	1 (1.27%)	2 (2.50%)
Nervous system disorders			
Dizziness	1 (1.28%)	1 (1.27%)	2 (2.50%)
Headache	4 (5.13%)	1 (1.27%)	5 (6.25%)
Somnolence	0 (0.00%)	1 (1.27%)	1 (1.25%)
Respiratory, thoracic and mediastinal disorders			
Nasal congestion	0 (0.00%)	1 (1.27%)	1 (1.25%)
Vascular disorders			
Hypotension	1 (1.28%)	0 (0.00%)	1 (1.25%)
Total	**20 (25.64%)**	**21 (26.59%)**	**38 (47.5%)**

N% = Number of subject reporting AE / number of subjects dosed with study products (x100)
Total N% = Number of subjects that reported at least one AE / number of subjects dosed with study products (x100)
Number of subjects dosed with study products: Test A - 78 subjects; Reference B - 79 subjects; Overall – 80 subjects
* Includes one subject with adverse event that began before initial patch application.

Reviewer's Comment: *There was a slightly higher incidence of blurred vision (8.97%, test and 5.06%, reference), dry mouth (7.69%, test and 6.33%, reference), and headache (5.13%, test and 1.27%, reference) while receiving the test patch application versus the reference product. These incidences are lower than the incidence reported in the RLD labeling, except for headache. For incidence of headache, they were all considered mild and possibly related to the study drug, and no adequate conclusion can be made from a single application.*

NDA 017874 labeling provides percent incidence of adverse event information for post-operative nausea and vomiting.[1]

Table 6-1 PONV: Adverse Drug Reactions in ≥3% of Patients

	Transderm Scōp (N=461)		Placebo (N=457)	
	n	%	n	%
Adverse Drug Reactions	303	65.7	259	56.7
Dry Mouth	133	28.9	72	15.8
Dizziness	57	12.4	33	7.2
Somnolence	36	7.8	16	3.5
Urinary Retention	33	7.2	30	6.6
Agitation	28	6.1	20	4.4
Visual Impairment	23	5.0	12	2.6
Confusion	18	3.9	14	3.1
Mydriasis	16	3.5	2	0.4
Pharyngitis	15	3.3	10	2.2

Visual impairment and dry mouth were reported at 5.0% and 28.9%, respectively for Transderm Scop®. Headache was not listed as an adverse event in ≥3% of patients.

Application site pruritus was similar between test (8.97%) and reference (8.86%) products.

2.6 Relevant Findings From Other Consultant Reviews

2.6.1 Review of the OSI Report

OSI inspection requested date	09/23/2014 REV-RPM-21(Primary Review) Original-1
Office of Scientific Investigations (OSI) Report Date	Pending at this time.
OSI inspection findings:	Pending at this time.

2.6.2 Review of the FDA Statistical Report (11/20/2014)

	Per Applicant	Per FDA
Overall conclusion	Demonstrates non-inferiority	**Does not** demonstrate non-inferiority
Adhesion performance	Pass per bootstrap method: $\mu_T - 1.25*\mu_R = -0.7930$ Fail per OGD method: upper bound of one-sided 95% confidence interval = 0.2977	**Fail (per OGD method)** upper bound of one-sided 95% confidence interval = 0.068
Additional Subject adjustments performed by the FDA statistician (e.g., non-parametric analysis)	N/A	No additional subject adjustment was made to the applicant's PP population.

See FDA statistical review for details.
https://panorama.fda.gov/PanoramaDocMgmt/document/download/090026f88085cb79

Subject Populations per FDA statistical reviewer:

Adhesion Analysis

The FDA's Per Protocol population is the same as the applicant's PP population.[4]

The FDA statistical reviewer identified main differences between applicant's analyses and FDA analyses as follows:

a. "The sponsor analyzed the sum cumulative adhesion score. The FDA statistician used the mean cumulative adhesion score.
b. The sponsor carried out a non-parametric analysis to compare the median of test versus reference using bootstrap approach. The FDA statistician did not repeat their analysis. The FDA statistician did not utilize a rank analysis.
c. The sponsor carried out a binary analysis for the proportion of patches that completely detached and concluded the test patch is non-inferior to the reference patch. In the FDA statistician secondary endpoint analysis for the difference in proportion for mean and by-visit scores, the test might exceed the reference by at most 1.7 and 2.1 percentage points with regard to the proportion of subjects who had mean and visit at hour 12 adhesion scores greater than 3 (full detachment). In OGD clinical review, the secondary endpoint results are used only as supplementary information."

[4] The 90/90 waiver consideration for high adhering patch does not apply for this ANDA. See attachment for details.

With regard to differences in proportions for mean by visits, the test patch may exceed the reference by at most 18.2 percentage points for the mean between products and 23.9 percentage points at hour 48 adhesion scores greater than 0. See below table for details.

Table 5: Analysis of the dichotomized adhesion score for score>crit versus others (N=77)*

Crit	0			1			2			3		
	b	c	UB	b	c	UB	b	c	UB	b	c	UB
Mean	17	13	**0.182**	4	6	0.054	1	4	0.021	0	2	0.017
Visit (Hour)												
12	4	1	0.099	0	1	0.021	0	1	0.021	0	1	0.021
24	8	5	0.129	0	2	0.017	0	2	0.017	0	2	0.017
36	16	7	0.230	1	4	0.021	0	4	0.003	0	4	0.003
48	18	9	**0.239**	3	4	0.056	1	5	0.012	1	5	0.012
60	17	12	0.192	4	8	0.034	2	7	0.011	1	7	-0.006
72	17	12	0.192	6	8	0.067	3	7	0.028	1	7	-0.006

*: Critical value (crit) was used to dichotomize the score.
b = number of subjects with a negative outcome (detachment, score>crit) using the test but not the reference;
c = number of subjects with a negative outcome (detachment, score>crit) using the reference but not the test.
UB (95% Upper Bound) for $P_T - P_R$ = P (mean cumulative/visit adhesion score greater than crit for test) - P (mean cumulative/visit adhesion score greater than crit for reference).

Reviewer's Comment: *From the clinical perspective, the applicant's adhesion data appears to be acceptable because the cumulative adhesion least-squares mean observed with the test product is lower than that of the reference product (0.2771 vs. 0.3247) and the frequency of adhesion score of 4 is less with the test product compared to the reference product (1 vs. 7). However, according to the FDA statistical analysis, the one-sided 95% upper confidence bound for the adjusted mean difference (μT -1.25μR) is greater than zero (0.068), not within the non-inferiority limit.*

Based on the proportion of patch applications with meaningful detachment evaluated in the new adhesion study (11325301), the proportion of patch application with a meaningful degree of detachment is no higher for the test product than for the reference product and detachment does not occur earlier in the application period for the test product than for the reference product. This is supported as follows:

- *a. A significantly higher number of reference product had an adhesion score of 4 (patch completely off the skin) compared to the test product (1 in the test group vs. 7 in the reference group).*
- *b. For the proportion of patch applications with meaningful detachment, defined as >50% detachment (score >2) per mean (i.e., a score of 0 and 1 vs. 2, 3 and 4), the FDA statistical reviewer concluded that the test patch might exceed the reference patch by at most 5.4 percentage points. For the proportion of patch applications with meaningful detachment, defined as > 25% detachment (score >1) per mean (i.e., a score of 0 vs. 1, 2, 3 and 4), the FDA statistical reviewer concluded that the test product might exceed the reference product by at most 18.2 percentage points.*
- *c. With regard to the time of detachment, the reference product had a score of 4 (patch completely off the skin) as early as at hour 12 but the test product had a score of 4 as early as at hour 48*

To support approval of this product based on adhesion assessment, the test product must show no clinically meaningful difference with regard to degree of detachment in addition to the mean adhesion scores.

Based on the applicant's pre-specified a non-parametric analysis to compare the median of the test product versus the reference product using the bootstrap methods, the applicant demonstrated that the test product was shown to be non-inferior to the reference product. It is questionable whether this statistical method is appropriate for evaluating adhesion performance between products because the median of adhesion scores would be most likely be zero in a bootstrap sample. The FDA statistical reviewer is concerned that this approach may loosen the current criterion for evaluating the adhesion performance.

The original PK study (PRG-604) was adequate to demonstrate bioequivalence between the test and reference products but this study was underpowered to meet the adhesion non-inferiority limit. As no overlay (tape) was used to improve adhesion, the fact that the test product demonstrated bioequivalence over a three-day wear period provides strong supportive evidence that any differences in adhesion between test and reference products were clinically insignificant.

2.7 Conclusion and Recommendation

2.7.1 Conclusion

The clinical data from a new adhesion study #11325301 in addition to previously reviewed data presented to ANDA 078830 are adequate to demonstrate that the adhesive performance of Perrigo R&D Company's Scopolamine Transdermal Extended Release Film, 1 mg/72 hr, is no worse than that of the reference drug product, Transderm Scop®, Transdermal Extended Release Film. The OSI inspection result for this study is still pending at this time.

2.7.2 Recommendations

From the DCR perspective, the new adhesion study (#11325301) and other previously reviewed data are adequate to support approval of this application.

CLINICAL BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

The Division of Clinical Review has no comment at this time.

APPEARS THIS WAY ON ORIGINAL

Attachment

From: Li, Huaixiang
Sent: Tuesday, December 09, 2014 7:57 AM
To: Tse, Sunny; Grosser, Stella C
Cc: Makhlouf, Fairouz; Kim, Carol Y
Subject: FW: ANDA 78830

Hi Sunny,

My concern for your question:
1. Yes. 90/90 rule does not apply for this study and no comments need to be included. I don't think we should put comment for 90/90 rule per each review since only 10% (even less) case happens.
2. No, the final statistical report doesn't need to be changed. I am not ready to put more comments for the sponsor's analysis since I don't have enough knowledge and experience for their analysis. OGD/OB patch working group has been working very hard for the challenge in the adhesion analysis issue. However, there is still long way to go. We don't even touch 'rank' analysis yet.

In addition, please check the forward email. I even don't know where this 'rank' analysis coming from for this study. I guess I only found bootstrap method, not rank method.

Thanks,
Helen

Review of Skin Irritation, Sensitization, And Adhesion Studies

ANDA# 078830 Scopolamine Extended-release Transdermal Film, 1 mg/72 hr Perrigo R & D Company

Dates of submissions reviewed:
February 23, 2007

Sarah H. Seung, Pharm.D.
Clinical Reviewer
Division of Clinical Review
Office of Generic Drugs

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Clinical Review for ANDA 078830

Executive Summary

I. Recommendation on Approval

The data submitted to ANDA 078830 are sufficient to demonstrate that the **skin irritation** potential of Perrigo R & D Company's (Perrigo's) placebo Scopolamine Extended-release Transdermal Film (Scopolamine patch) is no worse than that of a positive control (0.1% sodium lauryl sulfate (SLS)) of low irritancy. The data also demonstrate minimal potential of the placebo Scopolamine patch to induce **sensitization** as would be expected with use of the reference listed drug (RLD), Transderm Scop® (Novartis). However**, the data fail to demonstrate that the adhesive performance of Perrigo's Scopolamine patch is at least as good as that of the RLD**. Since adhesion performance is considered critical to both safety and efficacy, this application is **not** recommended for approval from a clinical bioequivalence perspective.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Scopolamine extended-release transdermal film is a prescription belladonna alkaloid used for the prevention of nausea and vomiting associated with motion sickness and recovery from anesthesia and surgery. It is an anticholinergic agent which acts as a competitive inhibitor of postganglionic muscarinic receptor sites of the parasympathetic nervous system, and on smooth muscles that respond to acetylcholine. The presumed mechanism of action is by cholinergic blockade in the CNS of the vestibular nuclei to higher centers in the CNS and from the reticular formation to the vomiting center.

ANDA 078830 is for a transdermal preparation of scopolamine. Perrigo conducted a skin irritation and sensitization study, enrolling 296 healthy subjects, to establish the irritation, adhesion and sensitization potential of their proposed Scopolamine patch. Perrigo also conducted a pharmacokinetic (PK/adhesion) study, enrolling 30 healthy subjects, during which the adhesion performance of their proposed transdermal film was also evaluated. In the skin irritation and sensitization study all subjects were randomized to receive a placebo version of Perrigo's Scopolamine patch and a positive control (0.1% sodium lauryl sulfate (SLS)). During the PK/adhesion study, all subjects received Perrigo's Scopolamine patch and the RLD, in a randomized crossover study design.

This review focuses on the studies submitted to ensure that the skin irritation and sensitization potential of the generic product are no greater than those of the RLD and that the generic product adheres to the skin as well as the RLD over the intended duration of wear.

B. Comparative Irritation

In the 296 subject irritation/sensitization study, the data from the placebo Scopolamine patch was compared to that of a positive control (0.1% SLS). The FDA statistical review confirmed that the study data showed the irritation potential of the placebo Scopolamine patch to be no worse than that of the positive control. The non-inferiority test was passed for the placebo Scopolamine patch versus the positive control.

C. Comparative Sensitization

Using the FDA's definition of a combined score of ≥2 at the last evaluation past the 24-hour observation (i.e., 48 hours or 72 hours) and challenge period scores higher than scores observed during the induction period, none of the subjects, in the 296 subject irritation/sensitization study, was considered potentially sensitized. Therefore, the potential of the placebo Scopolamine patch to induce sensitization would be minimal, as would be expected with use of the RLD.

D. Comparative Adhesion

In the 30 subject PK/adhesion study, the data from Perrigo's Scopolamine patch, 1 mg/72 hr, was compared to the RLD (Transderm Scop®). The FDA statistical review confirmed that **the mean adhesion score failed to demonstrate non-inferiority of the test product compared to the reference product**.

Based on the 95% upper confidence bound for the difference in proportions for mean and by visit scores, Perrigo's Scopolamine patch might exceed the RLD by at most 14.8 percentage points with regard to the proportion of subjects who had mean adhesion scores greater than or equal to 1 and at most 18.9 percentage points with regard to the proportion of subjects who had mean adhesion scores greater than or equal to 2.

E. Comparative Safety

The safety data submitted in this ANDA confirm that the test product did not cause any worse adverse events compared to the reference product.

Clinical Review

I. Introduction and Background

The Transderm Scop® (scopolamine extended-release transdermal film) system is a circular flat patch containing 1.5 mg of scopolamine base and designed to deliver approximately 1.0 mg of scopolamine over 3 days. It is indicated in adults for prevention of nausea and vomiting associated with motion sickness and recovery from anesthesia and surgery. The patch is to be applied only to skin in the postauricular area. Only one patch should be worn at any time, and the patch, which has a reservoir design, is not to be cut. One patch is to be applied for up to 72 hours and it can be replaced if necessary.

Scopolamine is a belladonna alkaloid with well-known anticholinergic properties. The most frequent adverse effect of transdermally administered scopolamine is dry mouth, occurring in about 29% of patients receiving the drug. Drowsiness (in 17% of patients), dizziness (in

12% of patients), disorientation, and confusion may occur with the use of scopolamine, creating a risk with activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery.

Less frequently, adverse CNS effects, including disorientation and memory disturbances, may occur with ordinary therapeutic doses of scopolamine. The most serious of these is acute toxic psychosis, including confusion, agitation, rambling speech, hallucinations, paranoid behaviors, and delusions.

Drug withdrawal symptoms, including nausea, vomiting, headache, dizziness, and disturbances of equilibrium, have been reported in some patients 24 hours or more after discontinuance of the transdermal system. Some of these symptoms may be related to adaptation to a motion-free environment from an environment in motion. More serious symptoms, including muscle weakness, bradycardia, and hypotension, also may occur following discontinuance of the transdermal system. Although mental confusion and dizziness may be observed with both acute toxicity and withdrawal, patients with withdrawal symptoms typically exhibit signs and symptoms of bradycardia, headache, nausea, abdominal cramps, and sweating, while tachyarrhythmias, dry skin, and decreased bowel sounds are suggestive of anticholinergic toxicity.

Given the safety concerns related to the use of scopolamine along with the usual short duration of therapy and the lack of adequate data regarding continuous use for periods of 21 days or longer, particularly with repetitive same-site applications, the skin irritation and sensitization studies recommended in the "Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products", which has been withdrawn, cannot be considered safe for either healthy volunteers or any patient population.

Delayed allergic contact dermatitis, manifested as pruritus and erythema at the site of application, has occurred with transdermal administration of scopolamine[1]. Skin irritation and sensitization studies conducted with the placebo patches will not provide a direct comparison to the actual reference product and will not rule out the possibility that an increase in irritation may occur when the drug substance is added. However, it is important to evaluate the adhesive components, which could also produce skin irritation and/or

[1] Gordon CR, Shupak A, Doweck I: Allergic contact dermatitis caused by transdermal hyoscine, BMJ 1989 298: 1220-1

sensitization and could result in a generic product being more irritating than the reference product.

An alternate approach might be comparative studies of skin reactions in patients randomized to use either the generic product or Transderm Scop® for the labeled indication and according to the labeled dosage and administration. Such a study would provide only very limited comparative information regarding skin irritation with the short-term use of the actual products and not the provocative same-site exposure that is usually required for dermal evaluation. The potential for sensitization could not be evaluated with such a study design.

A. Generic Drug Product

1. **Drug Established Name:** Scopolamine Extended-release Transdermal Film

2. **Drug Class:** Anti-Emetics

B. Reference Listed Drug (RLD)

1. **RLD Name:** Transderm Scop®

2. **NDA number:** 017874

3. **NDA Firm:** Novartis

4. **Date of approval:** December 31, 1979

5. **Approved Indication(s):**

   Transderm Scop® is indicated in adults for prevention of nausea and vomiting associated with motion sickness and recovery from anesthesia and surgery.

6. **Dose and Route of Administration**

   Initiation of Therapy: To prevent the nausea and vomiting associated with motion sickness, one Transderm Scop® patch should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. To prevent post operative nausea and vomiting, the patch should be applied the evening before scheduled surgery. To minimized exposure of the newborn baby to the drug, apply the patch one hour prior to cesarean section. Only one patch should be worn at any time. Do not cut the patch.

   Handling: After the patch is applied on dry skin behind the ear, the hands should be washed thoroughly with soap and water and dried. Upon removal, the patch should be discarded. To prevent any traces of scopolamine from coming into direct contact with the eyes, the hands and the application site should be washed thoroughly with soap and water and dried.

Continuation of Therapy: Should the patch become displaced, it should be discarded, and a fresh one placed on the hairless area behind the other ear. For motion sickness, if therapy is required for longer than 3 days, the first patch should be removed and a fresh one placed on the hairless area behind the other ear. For perioperative use, the patch should be kept in place for 24 hours following surgery at which time it should be removed and discarded.

The patch should be applied only to skin in the postauricular area.

7. Pertinent safety considerations

- Transderm Scop® is contraindicated in patients with angle-closure (narrow angle) glaucoma.
- Glaucoma therapy in patients with chronic open-angle (wide angle) glaucoma should be monitored and may need to be adjusted during Transderm Scop® use, as the mydriatic effect of scopolamine may cause an increase in intraocular pressure.
- Rarely, idiosyncratic reactions may occur with ordinary therapeutic doses of scopolamine. The most serious of these that have been reported are: acute toxic psychosis, including confusion, agitation, rambling speech, hallucinations, paranoid behaviors, and delusions.

C. Regulatory Background

1. INDs, Protocols, and/or Control Documents submitted by this sponsor

The sponsor submitted a Control Document (OGD# 05-1125), dated 9/2/05, requesting for the bioequivalence study requirements for this drug product. Comments, including recommendations regarding the skin irritation, sensitization and adhesion study, from the Division of Bioequivalence (DBE) were forwarded to the sponsor on 10/7/05. In response to the 10/7/05 comments, Perrigo submitted two protocols (OGD# 06-0332 dated 3/6/06 for skin irritation/sensitization/adhesion study and OGD# 06-0355/P06-070 dated 3/10/06 for the pharmacokinetic study) to OGD. Prior to receiving OGD's comments (OGD response dated 5/17/07) regarding their skin irritation/sensitization/adhesion study protocol, Perrigo conducted their studies (study dates 9/18/06 to 9/30/06 and 9/8/06 to 11/27/06) and submitted their ANDA (dated 2/23/07). The pharmacokinetic study protocol (OGD# 06-0355) was not reviewed because the ANDA was submitted prior to review.

Reviewer's comments: *The recommendations forwarded to the sponsor from DBE (dated 10/7/05) are consistent with the current recommendations found on the FDA website: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM179189.pdf (which contains more detailed recommendations) except for the dermal "other effects" scoring scale. Details of the difference in the "other effects" scoring scale is discussed in this review under section IV.C.4.g.iii: Dermatologic Evaluations (Cumulative Irritation). The sponsor did follow the recommendations provided to them.*

2. INDs, Protocols, and/or Control Documents submitted by other sponsors
Several protocols and controls have been submitted by other sponsors for this drug product.

There are 8 protocols from other sponsors in the Office of Generic Drug database:

Protocol No	Drug Name	Firm	Letter Date	Completed Date	Comments
96-016	Scopolamine TDS	(b) (4)			
98-005	Scopolamine				
98-006	Scopolamine				
02-059	Scopolamine				
04-030	Scopolamine				
04-037	Scopolamine				
05-032	Scopolamine				
06-085	Scopolamine TDS				

There are 14 Controlled Correspondence Documents from other sponsors listed in the OGD database:

Ctl No	Title	Description	Status	Doc Date	From
02-557	Transdermal Scopolamine	BA/BE Studies	(b) (4)		
03-093	Scopolamine Patch	Skin Irritation and Sensitization Studies			
03-717	Transdermal Scopolamine	Protocols for Skin Irrietation and			

Ctl No	Title	Description	Status	Doc Date	From
	Patch	Sensitization Studies for a Generic Transdermal Scopolamine Patch.	(b) (4)		
05-0492	Transdermal Extended Release Scopolamine Film	Dissolution Method and Bioequivalence Study Requirements	Closed 5/27/2005	4/27/2005	Perrigo Rx
05-0796	Scopolamine Transdermal Extended Release Film	Request guidance on the enclosed study protocols.	(b) (4)		
06-1037	Scopolamine Transdermal Patch	Meeting Request			
07-0544	Scopolamine Transdermal Patch	Advice regarding saftey concerns			
08-0119	Scopolamine Transdermal System	BE study			
08-0186	Scopolamine Transdermal System	Request for BE and dissolution recommendations			
08-0306	Scopolamine Transdermal Patch	BE recommendations			
11-0700	Scopolamine TDS	Query/follow-up regarding published literature.			

Reviewer's comments: *Some of the sponsors received the same comments as those given to Perrigo in OGD's correspondence dated 10/7/05. Prior to comments given to Perrigo, a less detailed advice was provided to other sponsors. However, more detailed comments were forwarded to sponsors in later years.*

3. Other ANDA submissions for same or related product

There are no approved ANDAs for this drug product. **This is a First Generic.**

DARRTS lists the following submissions for Scopolamine Transdermal System:

Application Type/Number	Submitter	Current Status	Status Date
[redacted] (b) (4)			

D. Other Relevant Information

1. [redacted] (b) (4)

2. Draft Guidance on Scopolamine Film, Extended Release/Transdermal, 1 mg/72 hr (October, 2011) posted on the FDA website: ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM179189.pdf***

Reviewer's comments: [redacted] (b) (4) *The* Draft Guidance on Scopolamine Film, Extended Release/Transdermal, 1 mg/72 hr (October, 2011) *represents the most recent recommendations of the OGD. The overall study designs for Perrigo's skin irritation and sensitization study and the pk/adhesion study are consistent with this Draft Guidance. However, some details of the two studies (e.g., numeric conversion of the skin "Other Effects" scores, definition of potentially sensitized and statistical analysis plan) are not consistent with the Draft Guidance. Details of these differences and their acceptability are discussed in this review under section IV.C:* Detailed Review of Skin Sensitization, Irritation, and Adhesion Studies.

II. Description of Clinical Data and Sources

A Multiple Site Study to Evaluate the Cumulative Skin Irritation and Sensitization Potential and Adhesive Properties of a Placebo Scopolamine Transdermal Delivery System (Modified Draize Test) [Protocol PRG-603]

A. CRO: Novum Pharmaceutical Research Services

B. Study Period

1. Date first subject dosed: September 8, 2006
2. Date last subject completed: November 27, 2006

C. Study Centers, Investigators and Enrollment

Site Number	Investigator	Location	Number enrolled
1	Shirley Ann Kennedy, M.D. Novum Pharmaceutical Research Services	Pittsburgh, PA	157
2	Soran Hong, M.D. Novum Pharmaceutical Research Services	Houston, TX	67
3	Daryl G. Ficklin, D.O. Novum Pharmaceutical Research Services	Las Vegas, NV	72

A Randomized, Two-Way Crossover Study to Evaluate the Bioequivalence, Tolerability and Adhesion of an Investigational Transdermal Scopolamine System Versus Transderm Scop® in Healthy Male and Female Subjects [Protocol PRG-604]

A. CRO

MDS Pharma Services
2350 Cohen Street
Saint-Laurent, Montreal
Quebec, Canada, H4R 2N6

B. Study Period

1. Period 1 Dosing: September 18, 2006
2. Period 2 Dosing: September 25, 2006
3. Last clinical procedure conducted on a subject: September 30, 2006

C. Study Centers, Investigators and Enrollment

Study Center: MDS Pharma Services, Quebec, Canada Fargo, ND
Principal Investigator: Gaetano Morelli, M.D.
Enrollment: 30 subjects

III. Clinical Review Methods

A. Overview of Materials Consulted in Review

1. Original Submission:
Original Submission dated February 23, 2007

2. Study Amendments
None

3. FDA Statistical Review:
Statistical Review by Huaixiang Li, Ph.D finalized on March 22, 2013.

B. Overview of Methods Used to Evaluate Data Quality and Integrity

Office of Scientific Investigations (OSI) Report

A request for investigation for Protocol PRG-603 was submitted on June 19, 2007. OSI conducted clinical site inspections on all three clinical sites (OSI review dated December 27, 2007). No forms FDA-483 were issued to any of the three sites. In addition, no issues were noted that would affect the integrity of the study data. OSI concluded that data from Study PRG-603 is acceptable for the Agency's review.

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

According to the study report, both studies were conducted in accordance with Good Clinical Practice (GCP) as contained in the US Code of Federal Regulations (21 CRF 50, 54, 56, 312 and 314) and the International Conference on Harmonization (ICH).

The protocol and informed consent form for PRG-603 was reviewed and approved by the Novum Independent Institutional Review Board (NIIRB) on August 15, 2006 prior to study commencement.

The protocol and informed consent form for PRG-604 was reviewed and approved by an Institutional Review Board convening at MDS Pharma Services in Montreal Quebec, Canada on July 25, 2006 prior to study commencement.

Reviewer's Comments:

The sponsor's studies appear to be in compliance with accepted ethical standards.

D. Evaluation of Financial Disclosure

The sponsor certified (Form FDA 3454) that the investigators involved in these studies did not have any financial arrangements, significant payments, proprietary interest or equity interest to report.

IV. Review of Skin Sensitization, Irritation, and Adhesion

A. Brief Statement of Conclusions

The data submitted to ANDA 078830 are sufficient to demonstrate that the **skin irritation potential** of Perrigo's placebo Scopolamine patch, is no worse than that of a positive control (0.1% SLS) of low irritancy. The data also demonstrate minimal potential of the placebo Scopolamine patch to induce **sensitization** as would be expected with use of the RLD. However, the data fail to demonstrate that the **adhesive performance** of Perrigo's Scopolamine patch is at least as good as that of the RLD, Transderm Scop®.

B. General Approach to Review of the Comparative Skin Sensitization, Irritation, and Adhesion

The sponsor conducted one clinical study and one pharmacokinetic/adhesion study. The clinical study (PRG-603) was reviewed to evaluate the irritation and sensitization properties of the proposed generic scopolamine extended-release transdermal film. The pharmacokinetic/adhesion study (PRG-604) was reviewed to evaluate the adhesion property of the proposed generic scopolamine extended-release transdermal film. The review of the pharmacokinetic data was conducted by the Division of Bioequivalence and is reported separately.

The paper submissions of the ANDA as well as the electronic submissions were reviewed in detail.

C. Detailed Review of Skin Sensitization, Irritation, and Adhesion Studies

A Multiple Site Study to Evaluate the Cumulative Skin Irritation and Sensitization Potential and Adhesive Properties of a Placebo Scopolamine Transdermal Delivery System (Modified Draize Test) [Protocol PRG-603]

1. **Sponsor's protocol:** PRG-603 (Novum Study No.: 10625308)

2. **Title:** A Multiple Site Study to Evaluate the Cumulative Skin Irritation and Sensitization Potential and Adhesive Properties of a Placebo Scopolamine Transdermal Delivery System

3. **Objective:** The primary objective of this study was to evaluate the potential for the scopolamine placebo patch to cause cumulative skin irritation and to induce sensitization, when applied over a continual 21 day period followed by a challenge application.

   A secondary objective was to evaluate the adhesive properties of the scopolamine placebo patch during a single application during the initial 72 hour application.

Reviewer's Comments: *Addition of the active drug could change the adhesive performance of the patch. Therefore, data from this placebo study provides only supportive information on the adhesive performance of the proposed product.*

4. **Study Design:**
   This study was a multiple site, multiple-application, challenge study in healthy subjects. The study consisted of two phases, an irritation/induction phase (Study Day 1 to Study Day 22) and a challenge phase (Study Day 36 to Day 41) to evaluate sensitization. A fourteen day rest period, during which no patches were applied, separated the two phases of the study.

Reviewer Comments: *The sponsor's overall study design is consistent with the* Draft Guidance on Scopolamine Film, Extended Release/Transdermal, 1 mg/72 hr (October 2011).

a. Treatments

Table 1.1: Treatment Arms

Article	Description
Test* (TRT A)	Placebo Scopolamine Transdermal Delivery System; Aveva Drug Delivery Systems, Inc. Lot No. 35411 Date of Manufacture: 06/19/2006
Mild Irritant** (TRT B)	0.05 ml of 0.1% sodium lauryl sulfate solution applied to Band-Aid® Perfect Blend™ clear bandages, 2.2 cm x 2.2 cm; Novum Pharmaceutical Research Services

* The test placebo patches were manufactured at a facility owned by Aveva Drug Delivery Systems, Inc.
** The mild irritant patches were prepared at each clinical site by designated personnel.

A member of the clinic staff who was not involved in any of the skin irritation grading assessments removed and applied the patches to each subject according to the randomization schedule.

During the first period of the applications (induction/irritation Phase, Day 1 through 22) the patches were applied to the same sites behind the subject's ear following the randomization schedule. During the irritation/induction phase, patches were applied and replaced on Days 1, 4, 7, 10, 13, 16 and 19. A window of ± 2 hours from the first patch application time was allowed for all assessments. After the last removal, on Day 22 all subjects underwent a 14 day rest phase when no patches were applied.

For the challenge application (Day 36), the same randomization was used. For example, if the subject received the test placebo patch behind the left ear in the induction/irritation Phase, it was placed on the left lower neck in the challenge phase. Only the test placebo patch was applied on Day 36. It was removed on Day 38, after 48 hrs (± 2 hours) of application.

Reviewer's Comments: *Due to limited space in the postauricular area, a negative control was not used during this study, which is consistent with the* Draft Guidance on Scopolamine Film, Extended Release/Transdermal, 1 mg/72 hr (October 2011).

b. Study population

Subjects who failed to complete the study were replaced to ensure that 200 subjects had evaluable data sets for the sensitization analysis. It was anticipated that up to 300 subjects would be enrolled to obtain at least 200 evaluable data sets.

i. **Inclusion Criteria**

(a) Adults aged 18 years of age or older.
(b) Females of child bearing potential must abstain from sexual intercourse or use a reliable method of contraception for at least 14 days prior to and throughout the duration of the study or a hormonal method of contraception for at least 30 days prior to the study and continue to use the same type of hormonal contraceptive during the study.
(c) Good health as determined by lack of clinically significant abnormalities in health assessments performed at screening.
(d) Signed and dated informed consent form, which meets all criteria of current FDA regulations.

Reviewer's comments: *The sponsor's inclusion criteria are acceptable.*

ii. **Exclusion Criteria**

(a) Presence of any current dermatological condition or history of skin sensitivity that would compromise the integrity of the study data.
(b) Excessive hair or other confounding factors (e.g. tattoos) at the application site that would compromise the ability of the patch to be applied or the ability of the evaluator to observe possible irritation.
(c) Use of systemic or topical analgesics, anti-inflammatory agents or antihistamines within 72 hours or systemic or topical corticosteroids within 21 days of the first patch application.
(d) Given birth or been pregnant within 3 months of the study start, currently pregnant, lactating or likely to become pregnant during the study.
(e) Unable or unwilling to make the required study visits.
(f) Receipt of study medication in another clinical study within 30 days of the first patch application.

Reviewer Comments*:*

- *The FDA generally recommends excluding patients with a history of significant dermatologic cancers except basal cell carcinomas that were superficial and did not involve the investigative site.*
- *The FDA generally recommends excluding patients with the presence of open sores at the application sites.*

c. Procedures/Observations

All procedures during this study were conducted on an out-patient basis. The study was conducted in two phases, an irritation/induction phase (Study Day 1 to Study Day 22) and a challenge phase (Study Day 36 to Day 41) to evaluate sensitization. A fourteen day rest period when no patches were applied separated the two phases of the study.

During the **irritation/induction phase** of the study, the test placebo and mild irritant patches were applied behind the study subjects' ears according to the randomization scheme. The same type of patch was applied on Days, 1, 4, 7, 10,

13, 16 and 19 to the same site behind the appropriate ear. Signs and symptoms of irritation were evaluated by trained, blinded, validated evaluators on each day the patch was replaced. Standardized rating scales were used for these evaluations and are provided below in this review under "Endpoints". To ensure the integrity of the study blind, a different evaluator, other than the observer performing the irritation ratings, recorded patch adhesiveness prior to the patch being removed. Following the removal of the patches on Day 22, all subjects underwent a 14 day rest period when no patches were applied.

In the **challenge phase** of the study the test placebo patch was applied on Day 36 to a naïve skin site on the lower neck at least 5 cm away from the site of application used during the irritation phase. The same side of the head was used. The patch was removed on Day 38 (48 hours after application). These areas were evaluated for possible skin sensitization effects at intervals over 72 hours after removal.

The degree of patch adhesion during the first patch application period (72 hours) was assessed at 24, 48, and 72 hours after application. During this period no tape or similar was applied to either the test placebo patch or the mild irritant patch. If a patch completely detached prior to a visit, the day the patch detached was recorded. The subjects were instructed to return within 24 hours to have a replacement patch applied. Those subjects who did not return within the required timeframe were dropped from the study. In order to assist in adhesion of the patch, following the first 72 hour patch application, hypoallergenic tape was allowed to be applied to the patches to ensure adherence to the site of application.

Table 1.2: Study Schedule

	Screening[1]	**Induction/Irritation Phase Study Days**				**Challenge Phase Study Days**	
Procedure	Day -28 → -1	Day 1	Days 2, 3 and 4	Days 4, 7, 10, 13, 16 and 19	Day 22	Day 36	Days 38-41
Informed Consent	X						
Medical History	X						
Physical Examination	X						
Vital Signs[2]	X						
Urine Pregnancy Test[3]		X				X	
Clinic Visit		X	X	X	X	X	X
Patch Application[4]		X		X		X	
Adhesiveness Assessment[5]			X				

Irritation Assessment[6]			X	X	X		
Sensitization Assessment[7]							X
Monitor and/or Record Adverse Events and Concomitant Meds		X	X	X	X	X	X

[1] Within 28 days of the first dose (Day 1) or can be performed on Day 1 prior to enrollment.
[2] Temperature, pulse, respiration and blood pressure were measured at the screening visit.
[3] For all female subjects regardless of child-bearing potential.
[4] Patches were applied for 72 hours in the Induction/Irritation Phase and for 48 hours in the Challenge Phase.
[5] At 24, 48 and 72 hours following first patch application.
[6] Approximately 30 minutes after patch removal.
[7] Approximately 30 minutes, 24, 48 and 72 hours after patch removal in the Challenge Phase

Reviewer Comments: *The sponsor's study procedures are consistent with the* Draft Guidance on Scopolamine Film, Extended Release/Transdermal, 1 mg/72 hr (October 2011).

d. Restrictions

i. **Prior and Concomitant Therapy**

The following concomitant medications were restricted while enrolled in the study unless otherwise allowed at the discretion of the Investigator:

(a) systemic or topical analgesics within 72 hours
(b) anti-inflammatory agents within 72 hours
(c) antihistamines within 72 hours
(d) systemic or topical corticosteroids within 21 days of the first patch application.

The subjects were questioned about their use of any prescription and over-the-counter (OTC) medications at each clinic visit. All concomitant medication use was recorded in the subject's source documentation.

ii. **Activities**

Subjects were requested to refrain from activities (e.g. extended swimming, excessive soaking of the site or steam baths/saunas) that may affect the integrity of a patch application.

Subjects were instructed not to apply any creams, lotions, powders or other topical products to the skin area where a patch was placed.

Reviewer's comments:

- *The sponsor's outlined restrictions are acceptable.*
- *None of the subjects in the sponsor's PP populations were on any restricted concomitant medication.*

e. Removal of Subjects from Therapy or Assessment

Subjects were advised that they were free to withdraw from the study at any time for any reason or, if necessary, the Investigator or sponsor could withdraw a subject from the study to protect the health of a subject. A subject could also be withdrawn for not complying with study procedures.

Subjects, who failed to complete the study, were replaced to ensure that 200 subjects had evaluable data sets in the PP population for the sensitization analysis.

f. Safety

Safety was evaluated by collection of adverse events. The collection of adverse events was done through both solicited and unsolicited means. Subjects were questioned about local events of itching, burning and stinging.

g. Endpoints

i. **Primary Variables**: The primary variables for this study were cumulative skin irritation and sensitization.

ii. **Secondary Variable**: The secondary variable for this study was to evaluate adhesion.

iii. **Dermatologic Evaluations** (**Cumulative Irritation**)

Approximately 30 minutes after patch removal on Days 4, 7, 10, 13, 16, 19 and 22, the application sites were observed for any signs of local irritation using the following rating scales:

When possible, the same evaluator performed all of the evaluations for a single subject throughout the study.

Table 1.3: Irritation Scoring

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

Table 1.4: Other Effects

0	No other observations
1	Slight glazed appearance
2	Marked glazed appearance
3	Glazing with peeling and cracking
4	Glazing with fissure
5	Film of dried serous exudates covering all or part of the patch site
6	Small petechial erosions and/or scabs

Reviewer's comment:
This is the same scoring system for other effects that has been generally accepted for skin irritation/sensitization evaluation, but the scale is different. The usual scale is A,B,C,F,G,H and begins with "Slight glazed appearance/peeling of skin observed". The letters are converted to numerical scores for analysis using the following scheme: A=0, B=1, C=2, and F,G, or H=3. Thus the other effects scoring system is as follows:

Table 1.5: Generally Accepted Other Effects Scoring System Compared to Sponsor's Scale

Sponsor Score	FDA Letter Score	FDA Numeric Score	Description
1	A	0	Slight glazed appearance/peeling of skin observed
2	B	1	Marked glazed appearance/peeling of skin observed
3	C	2	Definite peeling and cracking observed
4	F	3	Fissures observed
5	G	3	Film of dried serous exudates covering all or part of the patch site
6	H	3	Small petechial erosions and/or scabs

This change in the scale may impact the study results. Therefore, the FDA statistician was requested to analyze the sponsor's data using the FDA generally accepted scoring system.

iv. **Skin Sensitization Assessment**

On Day 38, assessments of the site of application were made at approximately 30 minutes, 24, 48 and 72 hours after the patch removal. The same rating scales as used for skin irritation were used. If at any evaluation after removal on Day 38 the scoring of irritation was greater than 4 on the dermal response scale and/or greater than 2 on the "other effects scale" then the subjects were considered to have demonstrated a potential sensitization response. Subjects must have completed at least the 24 hour return visit to be considered adequately observed for possible sensitization.

Reviewer's comments: *To be consistent with the usual analyses of skin sensitization studies, the Irritation score and the Other Effects score was combined for the FDA Sensitization*

analysis, using the following scores to replace the sponsor's proposed other effects scores: 0 or 1 = 0, 2 = 1, 3 = 2, 4 or 5 or 6 = 3.

According to the Draft Guidance on Scopolamine Film, Extended Release/Transdermal, 1 mg/72 hr (October 2011)*, a subject is considered potentially sensitized if all of the following criteria are met:*

(a) 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.
(b) The subject has a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last evaluation during the Challenge Phase.
(c) 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.

Ideally, all subjects with a potential sensitization reaction should have a re-challenge to confirm sensitization. No re-challenge was done for any subjects in this study.

v. **Adhesion Evaluations after First Patch Application**

The study staff evaluated the adhesiveness of the patches on Days 2, 3 and 4 using the following rating scale:

Table 1.6: Adhesion Scoring

0 =	≥90% 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 =	patch detached (patch completely off the skin)

Reviewer's comments: *The sponsor's adhesion scoring scale is consistent with the FDA recommended adhesion scoring scale.*

h. Statistical analysis plan

i. **Patient Populations**

The primary analysis for the irritation, sensitization, and adhesion utilized the Per Protocol (PP) populations.

(a) Cumulative Irritation
If a subject failed to complete all seven visits during the irritation/induction phase because they were discontinued early because of excessive irritation, they would be included in the PP population and their

Last Observation Carried Forward (LOCF) for future visits. In addition, subjects who did not return within 24 hours after a patch completely detached were dropped from the study.

Reviewer's comments:

- *The* Draft Guidance on Scopolamine Film, Extended Release/Transdermal, 1 mg/72 hr (October 2011) *defines the PP population for* ***cumulative irritation*** *analysis as follows: The test article 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) OR if a patch is moved or removed due to excessive irritation, it should be included using LOCF.*
- *The sponsor did not assign a numeric value for "excessive irritation". Although the sponsor included the discontinued patch type due to excessive irritation in the irritation PP population, the other patch type for the same subject was excluded from the irritation PP population. During this study, when a patch type was discontinued for excessive irritation, both patches (the placebo test and the mild irritant patch) for that particular subject were discontinued at the same time. The sponsor should have continued to apply the other patch type in order to include the other patch type in the irritation PP population. Five subjects* (b) (6) *discontinued early due to excessive irritation from the mild irritant patch. The mild irritant patch (Treatment B) for all but one subject* (b) (6) *is included in the sponsor's irritation PP population. The placebo test patch for all subjects is excluded from the irritation PP population. The mild irritant patch for subject* (b) (6) *should also be included in the irritation PP population using LOCF.*

(b) Sensitization

All subjects who completed at least one post patch removal reading and had at least an assessment made 30 minutes and 24 hours after patch removal would be included in the PP population for sensitization analysis. Their LOCF would be used if they failed to complete this part of the study. For example if a subject had their 30 minute and 24 hour assessments completed but failed to return for their 48 and 72 hour assessments then their 24 hour assessment would be carried forward for the 48 and 72 hour evaluations. If a subject had just the 30 minute assessment performed they would be included in the ITT population for sensitization only with no LOCF. If a subject missed the 24 hour assessment but returned for the 48 or the 72 hour assessment they would be included in the PP population. Any subject who after the patch was applied on Day 36 experienced local reactions that required the patch to be removed prior to Day 38 would be included in the PP population for sensitization with the assessment at the time of removal carried forward. Any subject who removed the sensitization patch for any other reason before Day 38 would be eligible for inclusion in the safety analysis only, but still would be eligible for inclusion in the irritation PP population.

Reviewer's comments: *The Draft Guidance on Scopolamine Film, Extended Release/Transdermal, 1 mg/72 hr (October 2011) defines the PP population for* ***sensitization***

analysis is as follows:

- *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 48, 48, and 72 hours after patch removal and be included in the sensitization analysis using LOCF.*

(c) Adhesion

To be eligible for inclusion in the PP population for patch adhesion a subject must have had the first patch applied and evaluated for three days, or if the patch fell off without deliberate interference, the subject/patch would also be included in the PP population for adhesion analysis.

Reviewer's comments: *Given that this study was not designed to compare the adhesive performance of the patches and a FDA statistical analysis on the adhesion data has not been requested, a definition for the PP population for adhesion analysis is not necessary.*

ii. **Cumulative irritation**

Primary analysis for the irritation phase of the study was performed on the PP population using the combined irritation and "other effects" score. Comparison of mean irritation was between the test placebo patch and the mild irritant patch (0.05 ml x 0.1% SLS) for the following values: irritation seen on Day 22 (following a cumulative 21 day application of the patch) and the total irritation score (sum of the irritation scores at all visits) on Day 22. The difference between the score for the test placebo patch and 1.25 times the mild irritant patch was calculated. If the upper 95% CI was less than zero, then the test placebo patch was considered to be no more irritating than the mild irritant patch used in the study.

Secondary analysis for the irritation phase of the study was performed on the PP population using the mean irritation score on Day 22 and the maximum irritation score on any study day during the 21 day application period.

Percentage of subjects with each grade of skin reaction on study Days 4, 7, 10, 13, 16, 19 and 22 was tabulated by patch type. In addition, the mean irritation score on Day 4, 7, 10, 13, 16, 19 and 22 for both patches was calculated. The mean irritation scores for the ITT population are presented for informational purposes.

Reviewer's comments:

- *The sponsor's statistical plan for cumulative irritation is appropriate. The relevant statistical analysis for the irritation evaluation is the upper bound of the one-sided 95% CI of*

the mean irritation score for Test Placebo Patch minus 1.25 times the mean score for Mild Irritant Patch (0.1% SLS), which must be less than or equal to zero to support approval of the application. In addition to this analysis of the cumulative irritation scores, the test product must not have a higher proportion of scores consistent with irritation response compared to the control.

- *To be consistent with the analysis of previous sensitization studies, the scores from "Other Effects" was added to the "Irritation Score", using the following adjustments: Other Effects Scores of 0 or 1 was converted to 0. A score of 2 was converted to 1. A score of 3 was converted to 2. A score of 4, 5, or 6 was converted to 3.*
- *Whereas the irritation scores are actually ordinal variables and not truly continuous variables, there is some concern that the cumulative scores may not provide the best comparison for all studies. Therefore, the FDA statistician was requested to also compare the Test Placebo Patch and Mild Irritant Patch with regard to the proportion of subjects that had mean cumulative irritation scores greater than 0 and also the proportion of subjects that had mean cumulative irritation scores greater than 1. The FDA statistician was also requested to compare the Test Placebo Patch and Mild Irritant Patch with regard to the proportion of individual patch applications with scores of 1 or greater and also the proportion of individual patch applications with scores of 2 or greater.*

iii. **Sensitization**

Only the test placebo patch was tested in the sensitization analysis. The data to investigate possible sensitization was generated from the Day 36 patch application scores only. If sensitization occurred after the Day 36 patch application but prior to Day 38 removal, the patch was removed and the assessment calculated from the time of patch removal. If at any evaluation after application on Day 36 the scoring of irritation was greater than 4 on the dermal response scale and/or greater than 2 on the "other effects scale" then the subjects were considered to have demonstrated a potential sensitization response.

The percentage of subjects with each grade of skin reaction was calculated from the 30 minute, 24, 48, and 72 hour evaluations after patch removal on Day 38 and tabulated by patch type. In addition, the mean irritation score at each of these readings for the test placebo patch was calculated.

The test groups' mean irritation scores at each post removal reading would be evaluated for potential skin sensitization.

The proportion of subjects who show a sensitization reaction to the test placebo patch would be presented.

Reviewer's comments: *See sensitization definition provided under Section* IV.C.4.g.iv*:* Skin Sensitization Assessment.

iv. **Adhesion**

Adhesiveness of the test placebo patch and the mild irritant patch was documented at 24, 48 and 72 hours after the first patches were applied. A listing of all complete patch detachments and descriptive statistics for the initial 72 hour application period was tabulated. A separate listing of all complete patch detachments for the entire study was tabulated.

Adhesiveness of the test placebo patch was documented at 24, 48 and 72 hours after the first patches were applied on Day 1. If a patch completely detached during this application period then the number of hours from when it was applied to when it detached was calculated. If a patch fell off at any time during the study then a new patch was to be applied within 24 hours of the detachment or else the subject was to be dropped from the study. If a subject removed a patch voluntarily between visits, this was not counted as a patch detachment but the subject was discontinued from further study participation.

A separate listing of all complete patch detachments was provided and descriptive data of the adhesion scores from each visit tabulated.

Reviewer's comments: *Given that the patches used in this study do not contain the active ingredient and there is no direct comparison to the RLD, the adhesion data from this study is only supportive. As supportive data it is important for the test product to demonstrate performance that is very close to that of the RLD in order to infer equivalence in clinical use. The FDA statistician has not been requested to perform statistical analysis on the adhesion data.*

5. Study Conduct

a. Discussion of compliance

A member of the clinic staff who was not involved in any of the skin irritation grading assessments applied and removed the patches to/from each subject according to the randomization schedule. Prior to each application, the site was cleaned according to the labeling instructions, using a dry tissue or similar. The location, date and time of application were recorded. If a patch completely detached prior to a scheduled visit, the day and time the patch detached was recorded. The subjects were instructed to return within 24 hours to have a replacement patch applied. Those subjects that did not return within the required timeframe were dropped from further study participation, with two exceptions. Two subjects (b) (6) had patches reapplied after the 24 hour re-application window and were not immediately dropped from the study. These subjects were not included in the PP population for the irritation analyses.

Reviewer's comments:

- *Seventy of the test placebo patches detached completely during the entire study (including the challenge phase).*

- *For both Subjects (b) (6), it was the mild irritant patch (TRT B) that detached and was not replaced within 24 hours. The subject should be excluded from the TRT B Irritation PP population as the sponsor stated. However, the subject should be included in the TRT A (placebo test) Irritation PP population.*
- *Three other subjects ((b) (6) for TRT B and (b) (6) for TRT A) were patch free for >24 hours. Their last patch application (#7) detached completely prior to 48 hours of wear and was not replaced. Therefore, these subjects should be excluded from the Irritation PP population for the corresponding treatment arm.*

b. Randomization/Blinding

Treatments were administered according to a randomization schedule. A randomization schedule was generated for each clinic site by the Biostatistics Department of Novum Pharmaceutical Research Services.

This study was not blinded to the subject or to those not involved in the performance of irritation assessment. To ensure the integrity of the study blind, a different evaluator, other than the observer performing the irritation ratings, recorded patch adhesiveness and removed and applied the patches, with one exception. For eight subjects at the Las Vegas clinical site, the Day 41 irritation assessment (during the challenge phase) was performed by an evaluator who had dosed these subjects earlier in the study. As only the test placebo patch was used in the sensitization phase, this did not affect the integrity of the study.

***Reviewer's comments**: Due to differences in appearance between the test patch and mild irritant, blinding of the observer/evaluator is difficult, especially for evaluation of patch adhesion, which requires direct observation of the patch itself. However, the sponsor made efforts to blind the evaluation of irritation during this study.*

c. Reserve Samples

Not applicable since only placebo transdermal patches were used during this study. However, retention samples have been retained at each clinic site under current FDA regulations (21 CFR, Sections 320.38 and 320.63).

d. Patient population (number included/excluded)

A total of 296 adult subjects were entered into this study and 228 subjects completed the study.

e. Protocol Deviation

There were a total of 145 protocol deviations documented and retained in the study files. These were mostly minor time deviations in the patch application and removal times.

The following deviations affected the PP populations:

- Ten subjects (b) (6) (b) (6) did not have the mild irritant patch applied on Day 10. These subjects were contacted and returned to the clinical site and had the

patches applied on Day 11, more than 24 hours after patch removal on Day 10.

- Six subjects [redacted] did not have the mild irritant patch applied on Day 10 and did not return to the clinical site to have the mild irritant patch applied.

Two sets of statistical analyses (one excluding these 16 subjects from the PP population and one including these 16 subjects in the PP population) were run on the data and are provided with the statistical report.

Reviewer's comments:

- *Since this is a placebo study, all adhesion data is considered as supportive information and is used to ensure adequate adhesion of the test articles to induce maximum irritation and sensitization potential.*
- *FDA **Irritation** PP **Exclusions** - The following test articles per subject need to be excluded in the Irritation PP population:*
  - *The 16 subjects who did not have the mild irritant patch (TRT B) applied on Day 10 (and were patch free for >24 hours) should be excluded from the TRT B Irritation PP population: [redacted].*
  - *The following subjects were patch free for >24 hours. Their last patch application (#7) detached completely prior to 48 hours of wear and was not replaced. Therefore these subjects should be excluded from the Irritation PP population:*
    - [redacted] *for TRT B only*
    - [redacted] *for TRT A only*
- *FDA **Irritation** PP **Inclusions** - The following test articles per subject need to be included from the Irritation PP population:*
  - *The mild irritant patch (TRT B) for subject [redacted] should also be included in the irritation PP population using LOCF.*
  - *For both Subjects [redacted] the mild irritant patch (TRT B) detached and was not replaced within 24 hours. The subject should be excluded from the TRT B Irritation PP population as the sponsor stated. However, the subject should be included in the TRT A (placebo test) Irritation PP population.*
- *FDA **Sensitization** PP **Exclusions** - The following subjects need to be excluded (and LOCF should not be used unless specified) from the Sensitization PP population:*
  - *Subject [redacted] was patch free for >24 hours during the induction phase. The last patch application (#7) detached completely prior to 48 hours of wear and was not replaced.*
  - *The following subjects had <45 hours of patch wear for the challenge patch due to the challenge patch detaching completely: [redacted]*
  - *Subject [redacted] is noted to have the challenge patch applied on 10/13/06 at 8:38am and the patch removed on the same date (10/13/06) at 9:01am. However, the 30-min skin assessment did not occur until 10/15/06. The CRF confirms the dates of patch application, removal and skin assessment.*
- *Data for Subjects [redacted] are not included in all of the sponsor's datasets. According to the CRFs, both subjects did not complete the study. Subject [redacted] completed up to 4 applications of the induction phase and Subject [redacted] did not complete the first*

application of the induction phase. Subject (b) (6) *adhesion scores for the first application are as follows: score of 0 at 24 hr, 0 at 48 hr, and 2 at 72 hour.*

- *The patient disposition for the sponsor's and FDA's populations are given in Table 1.7.*

Table 1.7: Patient disposition (per FDA Statistician)

	Test Placebo (TRT A)	**Mild Irritant (TRTB)**
Enrolled and Randomized	**296**	**296**
Sponsor's irritation PP population (IRRPPP)	**239**	**241**
Total exclusion from the sponsor's IRRPPP	57	55
Reason for exclusion from sponsor's IRRPPP		
Adverse event	8	5
Non-compliant	24	24
Voluntary withdrawal	25	25
No reason in the dataset[#]		1
Sponsor's sensitization PP population (SNSPPP)	**228**	
Total exclusion from the sponsor's SNSPPP	68	
Reason for exclusion from sponsor's SNSPPP		
Adverse event	10	
Non-compliant	29	
Voluntary withdrawal	27	
Other	2	
FDA's irritation PP population (IRRFPP)[**]	**240**	228
Total exclusion/inclusion from the FDA's IRRFPP population	56	68
Excluded in sponsor's IRRPPP	57	55
Didn't have patch applied on Day 10[*1]		12
Patch free for > 24 hours[*2]	1	2
FDA clinical reviewer recommend[*3]	+2	+1
FDA's SNS PP population (SNSFPP)	**220**	
Total exclusion from the FDA's SNSFPP population	76	
Excluded in sponsor's SNSPPP	68	
Subject had <45 hours of patch wear in challenge phase[@1]	7	
Records description[@2]	1	

Note; Patient may have multiple reasons to be excluded from the populations.

#: There was no explanation given in the electronic summary dataset for the exclusion of Subject (b) (6) (mild irritant) from the IRRPPP population. According to FDA clinical reviewer's comment, this subject didn't apply mild irritant patch at Day 10.

FDA clinical reviewer's comment:

**: There was a total of 246 subjects in the IRRFPP. There were 222 subjects who had both patches (Test and Mild irritant), 18 subjects who had only Test patch, and 6 subjects who had only Mild irritant patch.

*1: The 16 subjects who did not have the mild irritant patch (TRT B) applied on Day 10 and were patch free for >24 hours should be excluded from the TRT B Irritation PP population: (b) (6)

(b) (6). Subject (b) (6) were already excluded from the IRRPPP.
*2: Subject (b) (6) (TRT B), (b) (6) (TRT B), and (b) (6) (TRT A) were patch free for >24 hours.
*3: Subject (b) (6) (TRT B), (TRT A), and (b) (6) (TRT A) were included in the IRRFPP.
@1: Subject (b) (6) had <45 hours of patch wear for the challenge patch due to the challenge patch detaching completely.
@2: Subject (b) (6) is noted to have the challenge patch applied on 10/13/06 at 8:38am and the patch removed on the same date (10/13/06) at 9:01am. However, the 30-min skin assessment did not occur until 10/15/06.

6. Results

a. Subject Demographics

The 296 subjects participated in this study. Their demographic information is provided below.

Table 1.8: Subjects Demographic Characteristics (per sponsor)

Demographic Characteristics	N = 296
Gender (n,%)	
Male	92 (31.76%)
Female	202 (68.24%)
Race/Ethnicity (n,%)	
African American	170 (57.43%)
Caucasians	91 (30.74%)
Hispanic or Latino	24 (8.11%)
Hawaiian or other Pacific Islander	1 (0.34%)
Other	9 (3.04%)
Age (years)	
Mean ± Std	38.84 ± 12.44
Median	40
Min - Max	18-71

b. Irritation

Two sets of PP population statistical analyses were performed by the sponsor. The first set (Set 1) did not include 16 subjects who did not have the mild irritant patch applied on Day 10 as required by the protocol. The second set (Set 2) included these 16 subjects in the PP population.

The sponsor's primary analysis of interest was the comparison of the mean cumulative irritation seen on Day 22 between the test placebo patch and mild irritant patch and the total irritation score (sum of all visits) at Day 22.

According to the sponsor's analysis, the upper limits of the 95% CI for both the mean cumulative irritation score on Day 22 and the total cumulative irritation score over the entire 21 day period of application were both less than zero.

Table 1.9: PPP Analysis – Set 1 (per Sponsor)

	Test Placebo Patch	Mild Irritant Patch	Adjusted*	Upper 95% CI
Mean Cumulative Irritation (Day 22)	0.53 ± 0.79 N=225	0.88 ± 1.10 N=225	1.11 ± 1.37	-0.4029
Total Cumulative Irritation (sum of all visits)	2.71 ± 3.29 N=225	4.23 ± 4.88 N=229	5.28 ± 6.10	-1.817
*Mild irritant patch times 1.25				

Table 1.10: PPP Analysis – Set 2 (per Sponsor)

	Test Placebo Patch	Mild Irritant Patch	Adjusted*	Upper 95% CI
Mean Cumulative Irritation (Day 22)	0.54 ± 0.80 N=239	0.89 ± 1.09 N=237	1.11 ± 1.36	-0.4000
Total Cumulative Irritation (sum of all visits)	2.76 ± 3.34 N=239	4.39 ± 4.89 N=241	5.48 ± 6.11	-1.984
*Mild irritant patch times 1.25				

***Reviewer's comments**: According to the FDA statistician, the placebo patch was found to be non-inferior to the positive irritant control. The FDA statistician's results are provided below.*

Table 1.11: Analysis of the mean cumulative irritation scores using mixed model (per FDA Statistician)

Test placebo (LS mean μ_{TP})	Mild irritant (LS mean μ_{MI})	Upper limit one-sided 95% CB (μ_{TP} -1.25μ_{MI})	Pass the Non-inferiority test
0.3917	0.5482	-0.2323	Yes

Table 1.12: Frequency of irritation scores (per FDA Statistician)

Visit Day	Treatment	Score					
		0	1	2	3	4	6
Day 4	Test placebo	171	44	25			
	Mild irritant	164	45	17	1	1	
Day 7	Test placebo	180	48	12			
	Mild irritant	156	48	23	1		
Day 10	Test placebo	173	45	22			
	Mild irritant	140	55	27	2	3	1
Day 13	Test placebo	187	43	10			

Visit Day	Treatment	Score					
		0	1	2	3	4	6
	Mild irritant	152	52	20	3		1
Day 16	Test placebo	173	54	13			
	Mild irritant	148	44	29	3	3	1
Day 19	Test placebo	163	60	17			
	Mild irritant	135	50	34	4	4	1
Day 22	Test placebo	155	60	25			
	Mild irritant	116	69	30	8	4	1

Table 1.13: Frequency of maximum total irritation scores per each patch per subject (per FDA Statistician)

	0	1	2	3	4	6	Total
Test placebo	97	85	58				240
Mild irritant	71	80	60	11	5	1	228

Table 1.14: Frequency of mean cumulative irritation scores (per FDA Statistician)

	0	>0, <0.5	=0.5, <1	=1, <1.5	=1.5, <2	2	3	Total
Test placebo	97	75	35	27	4	2		240
Mild irritant	71	67	37	30	15	1	7	228

The FDA statistician also compared the placebo patch and the positive irritant control with regard to the proportion of subjects that had mean cumulative irritation scores greater than 0 and also the proportion of subjects that had mean cumulative irritation scores greater than 1. The FDA statistician also compared the placebo patch and the positive irritant control with regard to the proportion of individual patch applications with scores greater than 0 and also the proportion of individual patch applications with scores greater than 1. The placebo patch was found to be non-inferior compared to the positive irritant control for all of the analyses. The FDA statistician's results are provided in the following tables below.

Table 1.15: 95% Upper Confidence Bound based on Proportion of Subjects who had Mean Cumulative Irritation Scores >0 for the Test and Reference Patches (per FDA Statistician)

Score >0 for Test Placebo but Not for Mild Irritant	*Score >0 for Mild Irritant but Not for Test Placebo*	*Total Subjects*	*P_{TP}-P_{MI}**	*95% Upper Bound for P_{TP}-P_{MI}*		
				McNemar	*Clopper*	*Schuirmann*
8	*25*	*222*	*-0.0766*	*-0.0304*	*-0.0494*	*-0.0296*

**: P_{TP}=P (mean cumulative irritation score greater than 0 for test placebo), and P_{MI}=P (mean cumulative irritation score greater than 0 for mild irritant)*

Table 1.16: 95% Upper Confidence Bound based on Proportion of Subjects who had Mean Cumulative Irritation Scores >1 for the Test and Reference Patches (per FDA Statistician)

Score >1 for Test Placebo but Not for Mild Irritant	*Score >1 Mild Irritant but Not for Test Placebo*	*Total Subjects*	P_{TP}-P_{MI}*	*95% Upper Bound for P_{TP}-P_{MI}*		
				McNemar	*Clopper*	*Schuirmann*
1	*4*	*222*	*-0.0135*	*0.0075*	*-0.0037*	*0.0075*

**: P_{TP}=P (mean cumulative irritation score greater than 1 for test placebo), and P_{MI}=P (mean cumulative irritation score greater than 1 for mild irritant)*

Table 1.17: 95% Upper Confidence Bound on Proportion of Subjects with an Irritation Score >0 for Each Study Day for the Test and Reference Patches (per FDA Statistician)

	Score >0 for Test Placebo but Not for Mild Irritant	*Score >0 for Mild Irritant but Not for Test Placebo*	*Total Subjects*	P_{TP}-P_{MI}*	*95% Upper Bound for P_{TP}-P_{MI}*		
					McNemar	*Clopper*	*Schuirmann*
Day 4	*25*	*19*	*222*	*0.0270*	*0.0806*	*0.0526*	*0.0799*
Day 7	*17*	*29*	*222*	*-0.0541*	*0.0004*	*-0.0315*	*0.0007*
Day 10	*8*	*30*	*222*	*-0.0991*	*-0.0502*	*-0.0680*	*-0.0492*
Day 13	*14*	*34*	*222*	*-0.0901*	*-0.0352*	*-0.0605*	*-0.0344*
Day 16	*16*	*28*	*222*	*-0.0541*	*-0.0008*	*-0.0315*	*-0.0004*
Day 19	*18*	*31*	*222*	*-0.0586*	*-0.0026*	*-0.0350*	*-0.0022*
Day 22	*18*	*46*	*222*	*-0.1261*	*-0.0640*	*-0.0911*	*-0.0627*

**: P_{TP}=P (mean cumulative irritation score greater than 0 for test placebo), and P_{MI}=P (mean cumulative irritation score greater than 0 for mild irritant)*

Table 1.18: 95% Upper Confidence Bound on Proportion of Subjects with an Irritation Score >1 for Each Study Day for the Test and Reference Patches (per FDA Statistician)

	Score >1 for Test Placebo but Not for Mild Irritant	*Score >1 for Mild Irritant but Not for Test Placebo*	*Total Subjects*	P_{TP}-P_{MI}*	*95% Upper Bound for P_{TP}-P_{MI}*		
					McNemar	*Clopper*	*Schuirmann*
Day 4	*15*	*8*	*222*	*0.0315*	*0.0714*	*0.0584*	*0.0707*
Day 7	*6*	*17*	*222*	*-0.0496*	*-0.0099*	*-0.0280*	*-0.0096*
Day 10	*7*	*19*	*222*	*-0.0541*	*-0.0122*	*-0.0315*	*-0.0117*
Day 13	*5*	*16*	*222*	*-0.0496*	*-0.0115*	*-0.0280*	*-0.0111*
Day 16	*3*	*25*	*222*	*-0.0991*	*-0.0569*	*-0.0680*	*-0.0559*
Day 19	*6*	*28*	*222*	*-0.0991*	*-0.0528*	*-0.0680*	*-0.0516*
Day 22	*7*	*22*	*222*	*-0.0676*	*-0.0239*	*-0.0421*	*-0.0232*

**: P_{TP}=P (mean cumulative irritation score greater than 1 for test placebo), and P_{MI}=P (mean cumulative irritation score greater than 1 for mild irritant)*

c. Discontinuation of Patch

Not discussed by the sponsor.

Reviewer's comments: *Five subjects* [redacted] (b) (6) *discontinued early due to excessive irritation from the mild irritant patch (TRT B). No subjects are noted to have discontinued early due to excessive irritation for the placebo test patch (TRT A). The discontinuation of placebo test patch and the mild irritant has not been analyzed by the FDA statistician.*

d. Sensitization

In the sensitization phase of the study, none of the subjects demonstrated a sensitization response, defined as an irritation score greater than 4 and/or an "other effects" score greater than 2. The maximum irritation score recorded during the sensitization phase was 2 and the maximum "other effects" score was 0.

Reviewer's comments:

- *Using the sensitization definition previously provided, one subject (b) (6) appears to have had a potential sensitization reaction. Subject (b) (6) had an irritation score of 2 that persisted from 30 min to 72 hour post challenge patch removal. However, this subject presented the same reaction after the first and last applications of the placebo test patch during the induction phase. Therefore, this subject is deemed to have had an irritation reaction and not a sensitization reaction.*
- *According to the FDA statistician, none of the subjects were considered to be potentially sensitized. The FDA statistician's summary table is provided below.*

Table 1.19: Sensitization results for Placebo Test (per reviewer and FDA Statistician)

Score	Number of subjects with each score post challenge patch removal			
	30 min (N=220)	**24 hour (N=219[1])**	**48 hour (N=218[1])**	**72 hour (N=219[1])**
Irritation				
0	159	190	214	218
1	47	27	3	0
2	14	2*	1**	1**
Other Effects				
0	220	219	218	219

[1] *Irritation scores were missed for Subject (b) (6) at 24 hr, for Subjects (b) (6) at 48 hr and for Subject (b) (6) at 72 hr.*
**Subjects (b) (6) Subject (b) (6) scores at 48 hr was 1 and 72 hr was 0.*
*** Subject (b) (6)*

e. Adhesion

The overall mean adhesion score for the test placebo patch after the initial 72 hours of application was 0.40 (± 1.04). The mean adhesion scores for the test placebo patch at 24, 48 and 72 hours post-application were 0.10 (± 0.47), 0.20 (± 0.75) and 0.25 (± 0.75), respectively.

Over the first 72 hour application period, the test placebo patch detached 18 times (6.08% of first patches applied).

Reviewer's comments:

- *Since this is a placebo study, all adhesion data is considered as supportive information and is used to ensure adequate adhesion of the test articles to induce maximum irritation and sensitization potential.*

- *When a patch detached for the first application, a new patch was applied in order to keep the subject eligible for the cumulative irritation and sensitization analysis. The subsequent adhesion scores, reported in the datasets, after the replacement patch application was on the new patch.*
- *A frequency table for each adhesion score at each adhesion evaluation time for the first placebo test patch application using LOCF for those patches that detached is provided below.*
- *The NDA summary of all the clinical studies does not mention how many patches fell off during the study period.*
- *The FDA statistician has not been requested to analyze the adhesion data in this study.*

Table 1.20: Frequency of the First Application of the Placebo Test (N=282) for Various Adhesion Scores (0 - 4) at Various Evaluation Times (24 - 72 Hour) using LOCF for detached patches (per reviewer)

Score	Hour 24	Hour 48	Hour 72
0	266	253	234
1	9	16	26
2	4	2	4
3	1	0	2
4	2	11	16

A Randomized, Two-Way Crossover Study to Evaluate the Bioequivalence, Tolerability and Adhesion of an Investigational Transdermal Scopolamine System Versus Transderm Scop® in Healthy Male and Female Subjects (Protocol PRG-604)

1. **Sponsor's protocol#** PRG-604 (MDS Pharma Services Project AA31201)

2. **Title:** A Randomized, Two-Way Crossover Study to Evaluate the Bioequivalence, Tolerability and Adhesion of an Investigational Transdermal Scopolamine System Versus Transderm Scop® in Healthy Male and Female Subjects

3. **Objective**
   The primary objective was to compare the bioequivalence of an investigational scopolamine transdermal patch, releasing approximately 1.0 mg scopolamine over three days (72 hours), versus the reference product, TransdermScop®. The secondary objective was to evaluate the safety, tolerability and adhesion of the transdermal patches.

Reviewer's comments: *For the purpose of this review, only the adhesion, safety and tolerability data will be evaluated. The pharmacokinetic data has been reviewed by the Division of Bioequivalence.*

4. **Study Design**
   This was a single site, open-label, randomized, two-way crossover pharmacokinetic study conducted on 30 healthy adult subjects (15 males and 15 females) under fasting conditions. A total of 28 subjects (13 males and 15 females) completed the clinical phase of the study.

In each period, subjects were housed from approximately 12 hours before dosing until after the 120-hour post-dose events. Single 72-hour 1.0 mg scopolamine patch administrations were separated by a washout period of 7 days.

Reviewer Comments: *The sponsor's overall study design is consistent with the* Draft Guidance on Scopolamine Film, Extended Release/Transdermal, 1 mg/72 hr (October 2011).

a. Treatments

Table 2.1: Treatment Arms

Treatment	Description
Product A (Test)	Scopolamine Transdermal System 1.31 mg, 2.5 cm^2 Manufactured by: Aveva DDS, Inc.* Lot No.: 35409 Manufactured date: 07/26/06 (b) (4)
Product B (Reference)	TransdermScop®, 1.5 mg Manufactured by: ALZA Corporation. Distributed by: Novartis Consumer Health, Inc. Lot No.: 0526942** Expiration date: 08/08

* The drug product manufacturer is Aveva Drug Delivery Systems, Inc.
** bulk product Lot #20711701 as per Certificate of Conformance

On the morning of Day 1 of each period, subjects received a single dose of scopolamine transdermal system delivering approximately 1.0 mg over three days of either the test or reference formulation, according to the randomization scheme. All patches were applied to the skin behind each ear. The site of application was to be non-broken skin and free of cuts, scratches and abrasions. In addition, the site of application was not to have excessive hair or cover any recent tattoos or significant sunburn.

Approximately one hour prior to application, the site was gently cleansed with warm water only and allowed to air dry. No soaps or cleaning agents were used to clean the application site. The patch was applied immediately after removal from its outer package. Application was performed by one of the study staff by pressing the patch firmly into place and holding the patch on for approximately 30 seconds. No auxiliary tape or other substance was applied to the patch to maintain adhesion.

The patch was removed 72 hours (three days) after application. Any remaining adhesive was gently removed using warm water only and allowed to air dry; no soaps or other cleansing agents were used to clean the application site for at least 12 hours after patch removal.

b. Study population

i. Inclusion Criteria
Subject candidates fulfilled all of the following inclusion criteria to be eligible for participation in the study, unless otherwise specified:

(a) Healthy male and female subjects, 18-55 years of age.
(b) Subject had a Body Mass Index (BMI) between 22 and 30, inclusive.
(c) Subjects weight between 60 – 90 kg.
(d) Subject had signed the Informed Consent approved by an appropriate IRB.
(e) The subject was willing and able to understand the study procedures and able to communicate meaningfully with the study personnel.
(f) Female subjects of childbearing potential had to agree to use an acceptable method of contraception and had to keep the same method until at least 7 days following patch removal when having sexual intercourse with a non-sterile partner.
(g) The following screening laboratory parameters had to be within 5% of the normal range: CBC (excluding WBC) and urinalysis; and within 10% of the normal range: WBC, BUN, and creatinine. AST, ALT, and alkaline phosphatase had to be within normal limits. Bilirubin may be up to 10% above the upper limit of normal.
(h) Anti-HCV – negative
(i) Anti-Hbc and Anti-Hbs – negative [except in immunized individuals]
(j) Anti-HIV (HIV antibody test) – negative
(k) Urine drug screen – negative
(l) Serum pregnancy test (female subjects only) - negative
(m) The subject's skin at the site of application had to be non-broken and in good general condition

Reviewer's comments: *The sponsor's inclusion criteria are acceptable.*

ii. Exclusion Criteria
Subject candidates were not enrolled in the study if they met any of the following criteria:

(a) Routine consumption of any medication (prescription or OTC), vitamin, mineral, herbal or dietary supplement for one week before and during the study period.
(b) Used of any drug known to inhibit or induce drug metabolizing enzymes within 30 days prior to dosing.
(c) Consumption of grapefruit juice within 10 days of study drug administration.
(d) Pregnant (i.e. positive urine pregnancy test at screening) or lactating females or females planning to become pregnant.
(e) Presence of angle-closure (narrow angle) glaucoma determined by medical history.
(f) Presence of pyloric or other intestinal obstruction determined by medical history.
(g) Presence of urinary bladder neck obstruction determined by medical history.
(h) History of seizures or psychosis (including confusion, agitation, rambling speech, hallucinations, paranoid behaviors, and delusions).

(i) Blood pressure greater than 150/95 or below 95/65 mm Hg (sitting, measured at the screening examination).
(j) Hypersensitivity to scopolamine or to other belladonna alkaloids.
(k) History of allergic drug reactions or reactions to any component of the patch (e.g. adhesive, scopolamine).
(l) The subject had taken an investigation medication within 30 days prior to administration of study medication.
(m) The subject had any medical condition or instability that in the Investigator's opinion could adversely impact their participation, conduct of the study, or the collection of data.
(n) The subject had a history of drug, prescription or alcohol abuse within the past two years.
(o) An ECG abnormality considered to be clinically significant by the investigator.
(p) Subject must be cancer free at least three years (excluding squamous cell carcinoma and basal cell carcinoma).
(q) Subject must be at least one year disease free from squamous cell carcinoma and basal cell carcinoma.
(r) Donation of blood of 50 to 499 mL within 30 days or donation of greater than 499 mL of blood within 56 days of the study drug administration.

Minor deviations from these criteria were allowed only if the investigator and sponsor agreed in writing prior to subject enrollment.

Reviewer's comments: *The sponsor's exclusion criteria are acceptable.*

c. Procedures/Observations

In each period, subjects were housed from approximately 12 hours before dosing until after the 120-hour post-dose events.

Subjects were admitted to the study center on the evening before dosing (Day –1 of each period) and were screened for opiates, amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids and alcohol and a serum pregnancy test was performed for all female subjects..

After admission, subjects were randomly assigned to each treatment sequence, as per the randomization scheme.

On the morning of Day 1 for each period (Period 1: 9/18/2006 and Period 2: 9/25/2006), subjects received a single scopolamine transdermal system delivering 1.0 mg over three days. Patch applications were separated by a washout period of 7 days.

Blood samples (1 x 7 mL) were obtained from subjects prior to dosing (Hour 0), and for up to 120 hours post-dose. Blood samples were to be collected and processed as specified in the protocol.

Patch adhesion was evaluated within 10 minutes of each vital sign determination (i.e., every 12 hours) and within 10 minutes prior to patch removal during the wear period.

Application site evaluation was performed at approximately 30 ± 5 minutes and 24 ± 1 hour after the patch was removed.

Table 2.2: Study Design and Schedule of Assessments*

Assessments	Screen	Inpatient	Inpatient	Early Termination
	Day -30 – Day -1	Days -1 - 6	Days 7 – 13	
	Visit 1	Visit 2	Visit 3	
Informed Consent	X	X		
Inclusion/Exclusion Criteria	X	X	X	
Demographics	X			
Medical History	X			
Physical Examination	X			X
Vital Signs	X	X[a]	X[a]	X
ECG	X			
Clinical Labs	X		X	X
Serum Pregnancy Test (females only)	X	X	X	
Urine Drug Screen	X	X	X	
Concomitant Medications	X	X	X	X
Medication Administration		X[b]	X[b]	
Pharmacokinetic Sampling		X[c]	X[c]	
Adverse Event	X	X	X	X
Application Site Evaluation		X[d]	X[d]	
Patch Adhesion		X[e]	X[e]	
Discharge from Unit		X[f]	X[f]	X[f]

* There was a washout period of 4 days between patch removal and re-application (1 week between patch applications).

[a] Vital signs at pre-dose and every 12 hours during confinement

[b] Study medication applied on Days 1 and 8

[c] Plasma samples for scopolamine determinations were drawn at pre-dose, 2, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 48, 60, 72 (prior to patch removal), 74, 76, 78, 80, 82, 84, 96, 108, and 120 hours after patch application

[d] Approximately 30 minutes and 24 hours after the patch had been removed, the site of application was reviewed by a trained rater to assess skin irritation

[e] Patch adhesion was measured within 10 minutes of each vital signs determination during wear period

[f] Subjects discharged on Day 6, 13 or as a result of early termination

Reviewer Comments: *According to the* Draft Guidance on Scopolamine Film, Extended Release/Transdermal, 1 mg/72 hr (October 2011), *the recommended frequency for adhesion evaluation is "at least daily. Thus, the sponsor's adhesion evaluation of every 12 hours is acceptable.*

d. Restrictions

i. **Prior & Concomitant Medication**
Subjects were not allowed to take any medication (prescription or over-the-counter products), vitamins, mineral, herbal, or dietary supplements for the 7 days preceding the study, during the time of sample collection, and during the washout period between drug administrations. This prohibition did not include hormonal contraceptives.

Consumption of foods and beverages containing the following substances was prohibited as indicated:

- Xanthines: 24 hours prior to patch application and throughout the period of sample collection.
- Alcohol: 48 hours prior to patch application and throughout the period of sample collection.
- Grapefruit: 10 days prior to drug administration and throughout the study period.

If drug therapy other than that specified in the protocol was required, a decision to continue or discontinue the subject was made, based on the time the medication was administered and its pharmacology and pharmacokinetics.

ii. **Activities**
During the confinement period, the subjects were not allowed to engage in any strenuous activity. Subjects were to refrain from showering or bathing approximately 2 hours prior to patch application until the 24-hour post-dose sample, and for 12 hours after patch removal.

Reviewer's comments: *The sponsor's outlined restrictions are acceptable.*

e. Safety
Subjects were instructed to inform the study physician and/or nurse of any adverse events (AEs) that occurred during the study.

f. Removal of Subjects from Therapy or Assessment
Subjects were advised that they were free to withdraw from the study at any time for any reason. The Principal Investigator, sub-investigator or the Sponsor could remove a subject from the study to protect the health of a subject or for not complying with study procedures. If a subject withdrew from the study, all of the safety data normally required at the end of the study were obtained, if possible. Subjects experiencing AEs were followed until the AEs were resolved or lost to follow up.

g. Endpoints

i. **Adhesion Evaluations**
Patch adhesion was evaluated every 12 hours and was rated according to the scale below.

Table 2.3: Adhesion Scale:

0 =	90% 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 =	patch detached (patch completely off the skin)

Reviewer's comments: *The sponsor's adhesion scoring scale is consistent with the FDA recommended adhesion scoring scale.*

ii. **Irritation Evaluations**

The application site was assessed at approximately 30 ± 5 minutes and 24 ± 1 hour after patch removal for skin irritation and was rated according to the scales below:

Table 2.4: Irritation Scale:

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

Table 2.5: Other Effects:

0	No other observations
1	Slight glazed appearance
2	Marked glazed appearance
3	Glazing with peeling and cracking
4	Glazing with fissure
5	Film of dried serous exudates covering all or part of the patch site
6	Small petechial erosions and/or scabs

Reviewer's comments: *The sponsor's scoring system for "other effects" is slightly different from that generally accepted for skin irritation/sensitization evaluation. The usual scale is A,B,C,F,G,H and begins with "Slight glazed appearance/peeling of skin observed". The letters are converted to numerical scores for analysis using the following scheme: A=0, B=1, C=2, and F,G, or H=3. This change in the scale may impact the study results. However, since this study was not designed to evaluate cumulative skin irritation, the FDA statistician was not requested to analyze the irritation data from this study.*

h. Statistical analysis plan

i. Patient Population
Two analysis populations were used:

(a) Safety population included subjects who received at least one study medication including the investigative scopolamine patch and the Transderm Scop®.
(b) Pharmacokinetic population included all subjects who completed the study (wore both patches for three days) and who have an adequate number of data points to characterize the plasma concentration profile. It was expected that this excluded only those subjects who terminated study participation prior to completion.

Reviewer's comments: *The sponsor did not identify the patient population for adhesion analysis. The Per-Protocol (PP) population for 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 72-hour application.*

ii. Adhesion
The non-inferiority of the test product relative to the reference product was assessed by the sponsor with respect to % Adhesion. The sponsor converted scores to % Adhesion using the following formula:

% Adhesion = 1 - [Adhesion Sum]/24.

Where 24 represents the maximum achievable score based on patch fall-off observed at the first observation time point (12 hours) with this score carried forward for all remaining observations.

An ANOVA was performed by the sponsor on ln-transformed %Adhesion. The sponsor's ANOVA model included sequence, formulation and period as fixed effects and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term. Each ANOVA included calculations of LSM, the difference between formulation LSM and the standard error associated with this difference. The sponsor's above statistical analyses were performed using the SAS® GLM (version 8.2) procedure.

The lower bound of a one-sided 95% confidence interval on the ratio of geometric means was calculated by the sponsor by constructing first on the log scale a confidence interval on the difference of least-squares means (LSM), and then transforming the endpoints by anti-logarithm back to the original scale. The sponsor's determination of non-inferiority was based on whether the lower limits of the confidence interval for the ratio of LSM (expressed in %) was greater than 80%.

Reviewer's comments:

- *FDA statistician has been requested to analyze the mean cumulative adhesion scores, averaged over all observations in the application period, and carrying forward a maximum score for all patches that detached prior to the final observation. To support approval of the application, the 95% one-sided CI of the difference between the mean cumulative adhesion score for the test product minus 1.25 times the mean cumulative adhesion score for the reference product should be less than or equal to zero.*
- *The following adhesion data should be provided:*
  - *Frequency table showing the number of patches with each adhesion score at each evaluation time point*
  - *Number of patches that are completely detached at each evaluation time*
- *In addition, it is helpful to compare test vs. reference patches with regard to the proportion of patch applications with meaningful detachment, defined as ≥25% detachment (score ≥1) and also defined as ≥50% detachment (score ≥2).*

iii. Irritation
Not provided in the study report.

Reviewer's comments: *As previously mentioned, given that this study was not designed to evaluate cumulative skin irritation, the FDA statistician was not requested to analyze the irritation data from this study.*

iv. Safety
Not provided in the study report.

5. Study Conduct

a. Discussion of compliance
All study drugs were applied under the supervision of clinic personnel.

b. Randomization/Blinding
Subjects were randomized to receive the test and reference products according to the randomization scheme. This was an open-label study.

Reviewer's comments*: Given that the evaluation of patch adhesion requires direct observation of the patch itself, blinding of the observer/evaluator is difficult since there are differences in appearance between the test and reference patches.*

c. Reserve Samples
Not provided by the sponsor in the study report or study protocol.

Reviewer's comments: *The sponsor should refer to 21 CFR 320.38 and 320.63 regarding retention of study drug samples. For more information, the sponsor should refer to the Guidance for Industry: "Handling and Retention of BA and BE Testing Samples" (May 2004). Retention samples should be randomly selected from each drug shipment by each study site prior*

to dispensing the medication to subjects. Samples must be randomly selected at each investigational site where the medication is dispensed and retained by the investigator or an independent third party not involved with packaging and labeling of the study products. Retention samples should not be returned to the sponsor at any time.

d. Subject population (number included/excluded)
A total of 30 healthy adult subjects (15 males and 15 females) were enrolled in the study. Twenty-eight (28) subjects (13 males and 15 females) completed the clinical portion of the study and contributed to pharmacokinetic analyses.

Subject No (b) (6) was withdrawn as per Sponsor's request due to detachment of the patch on Day 2 of Period 2. Subject No. (b) (6) received the full dose of the Aveva scopolamine patch in Period 1, but was found to have lost his TransdermScop® patch during Period 2. Subject No. (b) (6) TransdermScop® patch was 90% adhered to the skin approximately 24 hours after dosing in Period 2, but it was missing from the site of application when checked again at 36 hours post-dose.

Subject No. (b) (6) was withdrawn by the Investigator due to adverse events after completion of Period 1.

Table 2.6: Protocol Deviations (Per Sponsor)

Subject No.	Deviation
(b) (6)	At screening, the hematology tests for monocytes were > 5 % allowable range for abnormal values. However, the subjects were placed on study. There was no impact on subjects' safety as per Principal Investigator.
	At screening, the urinalysis test for ketone level was > 5 % allowable range for abnormal values. However, the subject was placed on study. There was no impact on subject's safety as per Principal Investigator.
	At screening, the urinalysis test for blood was > 5 % allowable range for abnormal values. However, the subject was placed on study. There was no impact on subject's safety as per Principal Investigator.
	Subject consumed 1 glass of prune juice at 08:50 on 21 September 2006 and approximately 150 mL at 10:11 on 27 September 2006.
	Subject consumed 200 cc of prune juice at 09:45 on 21 September 2006, at 20:48 on 28 September 2006, and unknown amounts at 08:39 and 22:08 on 29 September 2006.

***Reviewer's comments**:*

- *The sponsor appropriately included Subject (b) (6) in the adhesion analysis. For Period II, A score of 4 should be carried forward from the 36 hour adhesion evaluation time for the Reference patch.*

- *The sponsor appropriately excluded Subject (b) (6) from Period II (Test) and appropriately included in Period I (Reference).*
- *None of the protocol deviations noted by the sponsor would affect the adhesion PP population or the adhesion analysis.*
- *No change to the sponsor's adhesion PP population is recommended by this reviewer.*

e. Subject Demographics (per sponsor)

Table 2.7: Demographic Characteristics of all enrolled subjects (per Sponsor)

Demographic Characteristics	
Gender	
Male	15 (50%)
Female	15 (50%)
Race/Ethnicity	
African American	1 (3.3%)
Caucasians	29 (96.7%)

	Age (years)	Weight (kg)	Height (cm)
N	30	30	30
Mean	40.7	72.9	167.9
Median	41.5	71.8	166.5
SD	8.1	8.8	9.1
Range	24-55	56.4-90.0	154-187

6. Results

a. Adhesion

The sponsor concluded that 90% of the subjects or more obtained adherence scores of 0 (90% adhered) or 1 (75% to less than 90% adhered) following treatment with the Test and Reference, regardless of time points. According to the sponsor's analysis, the ratio of LSM of the Test over Reference for the % adhesion was 97% with a lower 95% confidence interval limit of 91%.

Only one subject had a patch adhesion failure, occurring for Subject (b) (6) at approximately 36 hours after Reference patch application (Treatment B). In this subject, the Test (Treatment A) did not detach completely throughout the first study period. The frequency distributions of adhesion scores at each time point are shown in Table 14.3.5.

Mean adhesion, converted to percentage, was 87% for Test and 90% for Reference. The ratio of LSM of Test over Reference for the % adhesion was 97% with a lower 95% confidence interval limit of 91%.

Table 2.8: Number of Test (T, N=29) and Reference (R, N=30) Patches for Each Adhesion Scores at Each Evaluation Times (per sponsor)

Score	Hour 12		Hour 24		Hour 36		Hour 48		Hour 60		Hour 72	
	T	R	T	R	T	R	T	R	T	R	T	R
0	22	25	12	14	24	24	18	12	24	24	7	9
1	6	5	15	16	2	5	9	15	4	4	19	18
2	0	0	2	0	3	0	2	2	0	1	2	2
3	1	0	0	0	0	0	0	0	1	0	1	0
4	0	0	0	0	0	1	0	1	0	0	0	0

Table 2.9: Percentage of Test (T, N=29) and Reference (R, N=30) Patches for Each Adhesion Scores at Each Evaluation Times (per sponsor)

Score	Hour 12		Hour 24		Hour 36		Hour 48		Hour 60		Hour 72	
	T	R	T	R	T	R	T	R	T	R	T	R
0	75.9	83.3	41.4	46.7	82.8	80.0	62.1	40.0	82.8	82.8	24.1	31.0
1	20.7	16.7	51.7	53.3	6.9	16.7	31.0	50.0	13.8	13.8	65.5	62.1
2	0	0	6.9	0	10.3	0	6.9	6.7	0	3.4	6.9	6.9
3	3.4	0	0	0	0	0	0	0	3.4	0	3.4	0
4	0	0	0	0	0	3.3	0	3.3	0	0	0	0

Reviewer's comments:

- *The sponsor did not carry forward an adhesion score of 4 for patches that fell off prior to the 72 hour evaluation time in the above tables. Only 1 patch (Reference for Subject (b) (6) fell off during the entire study. For Subject (b) (6) the Reference patch fell off prior to the 36-hour evaluation time. A score of 4 is recorded for the 36-hour and 48-hour evaluation times. However, scores are not recorded for the 60-hour and 72-hour evaluation times. A score of 4 has been carried forward for these two evaluation times.*
- *The FDA statistician analyzed the adhesion data from this study. A frequency table for each adhesion score at each evaluation time is provided below.*

Table 2.10: Number of Test (N=29) and Reference (N=30) Patches with Each Adhesion Score at Each 12 Hour Interval (per FDA Statistician)

Score	*12 hour*		*24 hour*		*36 hour*		*48 hour*		*60 hour*		*72 hour*	
	Test	*Ref*	*Test*	*Ref*	*Test*	*Ref*	*Test*	*Ref*	*Test*	*Ref*	*Test*	*Ref*
0	*22*	*25*	*12*	*14*	*24*	*24*	*18*	*12*	*24*	*24*	*7*	*9*
1	*6*	*5*	*15*	*16*	*2*	*5*	*9*	*15*	*4*	*4*	*19*	*18*
2	*0*	*0*	*2*	*0*	*3*	*0*	*2*	*2*	*0*	*1*	*2*	*2*
3	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*1*	*0*	*1*	*0*
4	*0*	*0*	*0*	*0*	*0*	*1*	*0*	*1*	*0*	*1*	*0*	*1*

To support approval of the application, the 95% one-sided CI of the difference between the mean cumulative adhesion score for the test product minus 1.25 times the mean cumulative adhesion score for the reference product should be less than or equal to zero. ***The test patch was not found to be non-inferior to the reference patch for the mean cumulative adhesion score.*** *The FDA statistician's results are provided below.*

Table 2.11: Analysis for the Mean Cumulative Adhesion Scores using Mixed Model for the Test and Reference Patch (per FDA Statistician)

Test Patch LS mean (μ_T)	*Reference Patch LS mean (μ_R)*	*95% Upper Confidence Bound (μ_T - 1.25 μ_R)*	*Pass Non-inferiority Test?*
0.4711	*0.4944*	*0.1059*	*No*

In addition, the FDA statistician compared test vs. reference patches with regard to the proportion of patch applications with meaningful detachment, defined as ≥25% detachment (score ≥1) and also defined as ≥50% detachment (score ≥2). Based on the 95% upper confidence bound for the difference in proportions for mean and by visit scores, Perrigo's Scopolamine patch might exceed the RLD by at most 14.8 percentage points with regard to the proportion of subjects who had mean adhesion scores greater than or equal to 1 and at most 18.9 percentage points with regard to the proportion of subjects who had mean adhesion scores greater than or equal to 2. The FDA statistician's result are provided below.

Table 2.12: McNemar Confidence Bound on Proportion of Subjects with Patch Adhesion Score ≥ 1 (≥25% detachment) for Each Evaluation Time (per FDA Statistician)

	Score ≥1 for Test patch but Not for Reference patch	***Score ≥1 for Reference patch but Not for Test patch***	***Total Subjects***	***P_T-P_R****	***95% Upper Bound for P_T-P_R***		
					McNemar	*Clopper*	*Schuirmann*
Mean	*2*	*2*	*29*	*0.000*	*0.148*	*0.098*	*0.1407*
12 hr	*7*	*4*	*29*	*0.103*	*0.323*	*0.246*	*0.3019*
24 hr	*10*	*8*	*29*	*0.069*	*0.343*	*0.202*	*0.3230*
36 hr	*5*	*5*	*29*	*0.000*	*0.214*	*0.098*	*0.2028*
48 hr	*6*	*12*	*29*	*-0.207*	*0.060*	*-0.86*	*0.0674*
60 hr	*4*	*5*	*29*	*-0.034*	*0.170*	*-0.002*	*0.1628*
72 hr	*7*	*5*	*29*	*0.069*	*0.299*	*0.202*	*0.2803*

Note: Subject (b) (6) was excluded from the analysis of the dichotomized adhesion scores since the analysis required the subject to have scores for both the Test and Reference patches.

** P_T=P (mean cumulative/daily adhesion score ≥1 for test), and P_R=P (mean cumulative/daily adhesion score ≥1 for reference)*

Table 2.13: McNemar Confidence Bound on Proportion of Subjects with Patch Adhesion Score ≥ 2 (≥50% detachment) for Each Evaluation Time (per FDA Statistician)

	Score ≥2 for Test patch but Not for Reference patch	***Score ≥2 for Reference patch but Not for Test patch***	***Total Subjects***	***P_T-P_R****	***95% Upper Bound for P_T-P_R***		
					McNemar	*Clopper*	*Schuirmann*
Mean	*2*	*1*	*29*	*0.034*	*0.167*	*0.153*	*0.1885*
12 hr	*1*	*0*	*29*	*0.034*	*0.125*	*0.153*	*0.1885*
24 hr	*2*	*0*	*29*	*0.069*	*0.181*	*0.202*	*0.2325*
36 hr	*3*	*1*	*29*	*0.069*	*0.215*	*0.202*	*0.2325*
48 hr	*1*	*2*	*29*	*-0.034*	*0.098*	*-0.002*	*0.094*
60 hr	*1*	*2*	*29*	*-0.034*	*0.098*	*-0.002*	*0.094*
72 hr	*2*	*2*	*29*	*0.000*	*0.148*	*0.098*	*0.1407*

Note: Subject (b) (6) was excluded from the analysis of the dichotomized adhesion scores since the analysis required the subject to have scores for both the Test and Reference patches.

** P_T=P (mean cumulative/daily adhesion score ≥2 for test), and P_R=P (mean cumulative/daily adhesion score ≥ 2 for reference)*

b. Irritation

The sponsor concluded that the irritation results from the application site evaluation performed 30 minutes and 24 hours after patch removal were similar for both treatments, with more than 79% of the subjects presenting no evidence of irritation 24 hours after patch removal.

The site of patch application was observed for irritation 30 minutes and 24 hours after patch removal. At time 72.5-hour (ie. 30 minutes after patch removal), both treatments presented scores of 0 (No evidence of irritation), 1 (Minimal erythema, barely perceptible) or 2 (Definite erythema, readily visible, minimal edema or minimal papular response) only. According to the sponsor's analysis, 41.4% of the subjects in the test group obtained a score of 0, 44.8% a score of 1 and 13.8% a score of 2. The scores 0, 1 and 2 were obtained by 27.6%, 48.3% and 24.1% of the subjects in the reference group, respectively. At time 96-hour (ie. 24 hours after patch removal), 86.2% and 13.8% of the subjects obtained a score of 0 and 1, respectively for the test group. For the reference group, 79.3% of the subjects obtained a score of 0, 13.8% of the subjects obtained a score of 1 and 6.9% of the subjects obtained a score of 2.

Table 2.14: Percentage of Test and Reference Patches for Each Irritation and Other Effects Scores the Two Evaluation Times (per sponsor)

Score	Hour 72.5 (30 min post removal)		Hour 96 (24 hr post removal)	
	Test	Reference	Test	Reference
Irritation				
0	41.4	27.6	86.2	79.3
1	44.8	48.3	13.8	13.8
2	13.8	24.1	0	0
Other Effects				
0	86.2	96.6	100	100
1	13.8	3.4	0	0

"Other Effects Scoring": at time 72.5-hour, 86.2% of the subjects receiving Test obtained a score of 0 (No other observations) and 13.8% of the subjects obtained a score of 1 (Slight glazed appearance). Over 96.6% of subjects in Reference received a score of 0, whereas 3.4% received a score of 1. All subjects obtained a score of 0 for both treatments at time 96-hour.

Reviewer's comments: *Given that the subjects received only one application of each test material (i.e., test and reference), irritation data collected during this study provides limited information. Therefore, the FDA statistician has not been requested to analyze the irritation data from this study.*

D. Comparative Irritation Conclusion

In the 296 subject irritation/sensitization study, the data from the placebo Scopolamine patch was compared to that of a positive control (0.1% SLS). The FDA statistical review confirmed that the study data showed the irritation potential of the placebo Scopolamine patch to be no worse than that of the positive control. The non-inferiority test was passed for the placebo Scopolamine patch versus the positive control.

E. Comparative Skin Sensitization Conclusion

Using the FDA's definition of a combined score of ≥2 at the last evaluation past the 24-hour observation (i.e., 48 hours or 72 hours) and challenge period scores higher than scores observed during the induction period, none of the subjects, in the 296 subject irritation/sensitization study, was considered potentially sensitized. Therefore, the potential of the placebo Scopolamine patch to induce sensitization would be minimal, as would be expected with use of the RLD.

F. Comparative Adhesion Conclusion

In the 30 subject PK/adhesion study, the data from Perrigo's Scopolamine patch, 1 mg/72 hr, was compared to the RLD (Transderm Scop®). The FDA statistical review confirmed that the mean adhesion score failed to demonstrate non-inferiority of the test product compared to the reference product.

Based on the 95% upper confidence bound for the difference in proportions for mean and by visit scores, Perrigo's Scopolamine patch might exceed the RLD by at most 14.8 percentage points with regard to the proportion of subjects who had mean adhesion scores greater than or equal to 1 and at most 18.9 percentage points with regard to the proportion of subjects who had mean adhesion scores greater than or equal to 2.

IV. Comparative Review of Safety

A. Brief Statement of Conclusions

Given that the placebo study (PRG-603) did not compare the proposed test product to the Reference Listed Drug, the adverse events reported during that study reflect only the local skin effects of the inactive ingredients. All the treatment related adverse events were mild to moderate in severity.

During the adhesion study (PRG-604), where the active test and reference patches were compared, all of the reported adverse events were mild to moderate in severity. No serious adverse events or deaths occurred during this study.

The adverse events reported during the placebo and adhesion studies would not preclude the approval of this application.

B. Description of Adverse Events

A Multiple Site Study to Evaluate the Cumulative Skin Irritation and Sensitization Potential and Adhesive Properties of a Placebo Scopolamine Transdermal Delivery System (Modified Draize Test) [Protocol PRG-603]

Four adverse events (car accident, herniated disc surgery, food poisoning and hospitalization for shoulder and back pain) experienced by the subjects ((b) (6) (b) (6)) during this study were judged as serious and unrelated to the study patches.

Local changes at the site of patch application was not considered as adverse events, unless in the opinion of the investigator they were significant to the point where it would be inappropriate to continue the subject in the study then the subject would be discontinued for safety reasons. Signs or symptoms of irritation such as burning, itching and pain were reported as adverse events. When possible, adverse events were attributed to either the test placebo or the mild irritant patch. Non-localized adverse events that could not be attributed to either patch were classified as unknown.

The most frequently reported adverse event was pruritis. There was a statistically significant difference between the number of subjects reporting pruritis by patch type (p=0.0003, Mantel-Haenszel Chi-Square). Pruritis was reported by 3.38% of subjects for the test placebo patch and by 11.15% of subjects with the mild irritant patch (0.1% SLS).

No deaths occurred during this study.

Reviewer's comments: *There were 141 AEs reported by 77 subjects during this study. Of the 141 AEs, 61 were probably or possibly related to the study patches. All AEs were mild to moderate in severity except for three (car accident, herniated disc surgery and food poisoning). There were 62 (13 test placebo and 49 mild irritant) application site related AEs. Application site related AEs consisted of blister, ear pruritis, inflammation, neck pain, edema, pain, pruritus, rash, popular rash, skin burning sensation, skin irritation and skin ulcer.*

A Randomized, Two-Way Crossover Study to Evaluate the Bioequivalence, Tolerability and Adhesion of an Investigational Transdermal Scopolamine System Versus Transderm Scop® in Healthy Male and Female Subjects (Protocol PRG-604)

The frequency of adverse events (AEs) by subject and number of AE reports are summarized below in Table 12.2.1.

Table 3.1: Summary of Adverse Events by Treatment Groups (per Sponsor)

Treatment	Number (%) of subjects with AEs	Number of AEs reported
Test (A) (n = 29)	22 (75.9%)	61
Reference (B) (n = 30)	25 (83.3%)	96
Overall (n = 30)	27 (90%)	157

There were no deaths or other serious AEs in this study. All AEs were considered mild or moderate. Table 14.3.1.3 summarizes adverse event severity and relationship to study treatment by the number of events.

Table 3.2: Number (%) of Adverse Events by Severity and Relationship to Study Drug

Treatment	Severity		Relationship to Study drug			
	Mild	Moderate	Definitely	Possibly	Unlikely	Not related
Test (A)	57 (93.4%)	4 (6.6%)	21 (34.4%)	18 (29.5%)	9 (14.8%)	13 (21.3%)
Reference (B)	79 (82.3%)	17 (17.7%)	22 (22.9%)	30 (31.3%)	32 (33.3%)	12 (12.5%)

Of the 157 AEs reported, 38 (24.2%) were application site erythema, judged definitely treatment related. Five more AEs (all were glazed appearance at the application site) were definitely treatment-related, forty-eight AEs (30.6%) were possibly treatment-related, and the remaining 66 AEs (45.2%) were either unlikely or not related to the study medication.

The most frequently occurring AE was application site erythema, observed in 80% of subjects (58.6% Test, 70.0% Reference). Other events occurring in 10% of subjects or more were headache, blurred vision, dry mouth, nausea, application site reaction (glazed appearance), dry throat, dizziness, vomiting, mydriasis, and vessel puncture site bruise (see Table 12.2.3:1). All remaining AEs were reported by 2 subjects (6.7%) or less.

Table 3.3: Frequently Reported Adverse Events (occurring in at least 10% of subjects) by Number (%) of subjects (per Sponsor)

Adverse Event	Test (A) (n = 29)	Reference (B) (n = 30)	Overall (n = 30)
Application site erythema	17 (58.6%)	21 (70.0%)	24 (80.0%)
Headache	5 (17.2%)	7 (23.3%)	11 (36.7%)
Blurred vision	5 (17.2%)	5 (16.7%)	8 (26.7%)
Dry mouth	3 (10.3%)	3 (10.0%)	6 (20.0%)
Nausea	3 (10.3%)	4 (13.3%)	5 (16.7%)
Application site reaction*	4 (13.8%)	1 (3.3%)	5 (16.7%)
Dry throat	3 (10.3%)	2 (6.7%)	5 (16.7%)
Dizziness	2 (6.9%)	2 (6.7%)	4 (13.3%)
Vomiting	0	3 (10.0%)	3 (10.0%)
Mydriasis	3 (10.0%)	0	3 (10.0%)
Vessel puncture site bruise	3 (10.0%)	0	3 (10.0%)

** Reviewer's comment: application site reaction consisted of "glazed appearance at patch application site".*

Application Site Adverse Events

The number of subjects with AEs occurring at the application site is summarized in Table 12.2.3.1:1, below.

Table 3.4: Number (%) of Subjects with Adverse Events occurring at the Application Site (per Sponsor)

Adverse Event	Test (A) (n = 29)	Reference (B) (n = 30)	Overall (n = 30)
Application site erythema	17 (58.6%)	21 (70.0%)	24 (80.0)
Application site reaction*	4 (13.8%)	1 (3.3%)	5 (16.7%)
Application site pruritus	0	2 (6.7%)	2 (6.7%)

* *Reviewer's comment: application site reaction consisted of "glazed appearance at patch application site".*

Application site AEs were mild and generally resolved without concomitant therapy.

Application site erythema was the most frequently observed application site AE. Application site erythema was definitely treatment related. When present, it was observed approximately 30 minutes post-dose and resolved by 24 hours after patch removal.

Five subjects had an application site reaction (glazed appearance at application site) definitely related to the study medication and that was observed approximately 30 minutes post-dose (i.e. after patch removal) and resolved within 24 hours without concomitant therapy for all subjects.

Subjects (b) (6) reported mild pruritus following dosing with the Reference. For Subject (b) (6), pruritus was reported 2.5 days after application but was deemed unlikely to be related to study medication. Pruritus resolved after 2.4 days, without concomitant medication. For Subject (b) (6) pruritus was one of several symptoms that required concomitant treatment (see Adverse Events Leading to Subject Withdrawal below). Pruritus began 1 day post-dose, was possibly related to study medication and resolved 5 days post-dose.

Adverse Events Leading to Subject Withdraw

One subject was removed from the study due to an adverse event. Subject (b) (6) is a 42 year-old Caucasian man who developed an allergic-type reaction in study Period 1 following application of the Reference patch. The subject reported mild blurred vision, dry mouth, dry throat, pruritus, eye pruritus, ocular hyperaemia, erythema and eye swelling the next day. All aforementioned adverse events were possibly treatment-related. Mild application site erythema was definitely treatment-related, and was reported 72.5 hours post-patch application. All adverse events, but application site erythema, were resolved at the time of discharge. The Subject was discontinued from the study due to AEs and was not dosed in Period 2.

V. Relevant Findings From Division of Scientific Investigations, Statistics and/or Other Consultant Reviews

A. Office of Scientific Investigations (OSI)

A request for investigation for Protocol PRG-603 was submitted on June 19, 2007. OSI conducted clinical site inspections on all three clinical sites (OSI review dated December 27, 2007). No forms FDA-483 were issued to any of the three sites. In addition, no issues were noted that would affect the integrity of the study data. OSI concluded that data from Study PRG-603 is acceptable for the Agency's review.

B. Statistics

The FDA statistical review (by Huaixiang Li, finalized on March 22, 2013) had the following conclusions:

Irritation Analysis
The FDA statistician concluded that the test placebo patch was non-inferior to the mild irritant control with regard to the primary endpoint of mean cumulative irritation scores. The FDA statistician also concluded that test placebo patch was non-inferior to the mild irritant control with regard to the secondary dichotomized endpoints defined as the proportion of subjects with mean cumulative irritation score > 0 and >1 and the proportion of subjects with irritation scores > 0 and >1 for each day.

Sensitization Analysis
Using the definition of a combined score of ≥ 2 at the last evaluation at 48 hours or 72 hours and challenge period scores higher than scores observed during the induction period, none of the subjects were identified as being potentially sensitized to test placebo patch.

Adhesion Analysis
The FDA statistician concluded that the test patch **failed** to demonstrate non-inferiority to the reference product with regard to the primary endpoint of mean cumulative adhesion scores.

Based on the 95% upper confidence bound for the difference in proportions for mean and by visit scores, Perrigo's Scopolamine patch might exceed the RLD by at most 14.8 percentage points with regard to the proportion of subjects who had mean adhesion scores greater than or equal to 1 and at most 18.9 percentage points with regard to the proportion of subjects who had mean adhesion scores greater than or equal to 2.

VI. Formulation

A. Generic Drug Product Design

The placebo patch has been designed to mimic the performance of scopolamine patch as closely as possible. The scopolamine patch is a (b) (4)

(b) (4)

(b) (4)

All patches will be manufactured by Aveva Drug Delivery Systems, Inc., (b) (4) (b) (4) in Miramar, Florida.

B. RLD Product Design

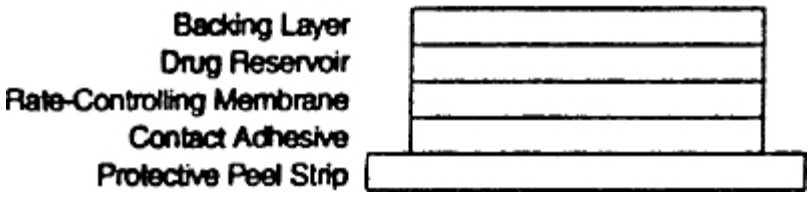
Transderm Scop® is a prescription drug available in one strength, 1 mg/72 hr. Each Transderm Scop® system contains 1.5 mg of scopolamine and is designed to deliver *in-vivo* approximately 1.0 mg of scopolamine over 3 days. Transderm Scop® is available in packages of 4 patches. Each patch is foil wrapped.

Transderm Scop® is a tan-colored circular patch, 2.5 cm^2, on a clear, oversized, hexagonal peel strip, which is removed prior to use. It is a 0.2 mm thick film with four layers. Proceeding from the visible surface towards the surface attached to the skin, these layers are:

a. A backing layer of tan-colored, aluminized, polyester film;
b. A drug reservoir of scopolamine, light mineral oil, and polyisobutylene;
c. A microporous polypropylene membrane that controls the rate of delivery of scopolamine from the system to the skin surface; and
d. An adhesive formulation of mineral oil, polyisobutylene, and scopolamine.

A protective peel strip of siliconized polyester, which covers the adhesive layer, is removed before the system is used. The inactive components, light mineral oil (12.4 mg) and polyisobutylene (11.4 mg), are not relased from the system.

Cross section of the system:



C. Components & Composition

Table 4.1: Test and RLD Formulations

Ingredient	Function	Test		Reference*
		mg/2.5 cm^2 Patch	% w/w	mg/2.5 cm^2 Patch
Scopolamine Base	Active	(b) (4)		(b) (4)

Reviewer's Comments: *The test patch is qualitatively and quantitatively different than the reference patch. These qualitative and quantitative differences are acceptable at the levels listed from a regulatory perspective, as determined by the filing review from the Regulatory Support Branch. The inactive ingredients are below the Inactive Ingredients Database limit or conform to previously accepted excipient usage. The adverse events reported during these studies show no apparent effect of the formulation differences on product safety. However, the adhesive performance of the proposed patch will contribute to the overall efficacy and safety profiles of the product. Incomplete adhesion could lead to lower efficacy and possibly use of an additional patch.*

VII. Conclusion and Recommendation

A. Conclusion

The data submitted to ANDA 078830 are sufficient to demonstrate that the **skin irritation** potential of Perrigo R & D Company's (Perrigo's) placebo Scopolamine Extended-release Transdermal Film (Scopolamine patch) is no worse than that of a positive control (0.1% sodium lauryl sulfate (SLS)) of low irritancy. The data also demonstrate minimal potential of the placebo Scopolamine patch to induce **sensitization** as would be expected with use of the reference listed drug (RLD), Transderm Scop® (Novartis). However, **the data fail to demonstrate that the adhesive performance of Perrigo's Scopolamine patch is at least as good as that of the RLD**.

B. Recommendation

From a clinical bioequivalence perspective, this application is **not** recommended for approval.

OFFICE OF GENERIC DRUGS CLINICAL REVIEW

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 078830 APPLICANT: Perrigo R & D Company

DRUG PRODUCT: Scopolamine Extended-release Transdermal Film, 1 mg/72 hr

The following deficiencies listed below may be delivered via the easily correctable deficiency method (10 day firm response expected) if the situation allows ___ YES __X__NO

The Division of Clinical Review has completed its review and the following deficiencies has been identified:

1. You have not provided adequate data to ensure that the adhesive performance of your product is at least as good as that of the RLD.

   In the pharmacokinetic/adhesion study (PRG-604), your product was statistically significantly less adhesive than the reference product. The study failed to show non-inferiority of your Scopolamine Extended-release Transdermal Film to the reference product with regard to adhesion performance.

2. For future bioequivalence studies (including test-reference comparisons of skin irritation, sensitization, and adhesion), the final study report must include a discussion of the retention of testing samples. Please refer to 21 CFR 320.38 and 320.63 regarding retention of study drug samples. For more information, please refer to the Guidance for Industry: "Handling and Retention of BA and BE Testing Samples" (May 2004). Retention samples must be randomly selected from each drug shipment by each study site and retained by the investigator or an independent third party not involved with packaging and labeling of the study products. Retention samples are not to be returned to the sponsor at any time. If these recommendations are not followed for future bioequivalence studies, then the study may be found unacceptable to support product approval. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, "Good Clinical Practice: Consolidated Guideline."

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 page}

Ethan Stier, Ph.D.
Acting 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/

NITIN K PATEL on behalf of SARAH H Seung
05/14/2013

JOHN R PETERS
05/15/2013

ETHAN M STIER
05/17/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78830

CHEMISTRY REVIEWS

A. Check List

Solid IR/Oral Sol. RPN < 60 or Injection/Ophthalmic Q1/Q2 = RLD – 2 Tier	☐
First Generic – 3 Tier	☐
Other Criteria under "Exceptions List" for Table 1 of SOP – 3 Tier	☒

B. Approvability: – CMC is adequate, EES and labeling pending.

ANDA 78830

Scopolamine Transdermal Therapeutic System 1 mg/3 days

Perrigo R&D Company

CR #5

Guohua Li, Ph.D.
Chemistry Division V

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Chemistry Assessment **18**

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S DRUG SUBSTANCE 18

Chemistry Review Data Sheet

1. ANDA: 78830

2. REVIEW #: 5

3. REVIEW DATE: 07/11/2014, 08/22/2014

4. REVIEWER: Guohua Li, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	February 23, 2007
Amendment	May 11, 2007
Review #1	July 20, 2007
Minor Amendment	January 4, 2008
Review #2	April 4, 2008
Minor Amendments	April 16 and 17, 2012 June 7, 2012
Review #3	July 2, 2012
Minor Amendment	August 13&14, 2012
Unsolicited Amendment	March 19, 2013
Review #4	April 05, 2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	03/14/2014
Amendment	08/19/2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Perrigo R&D Company
Address:	515 Eastern Avenue Allegan, MI 49010
Contact:	James Chambers
Telephone:	269-673-8451
Fax:	269-673-7655

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA

b) Non-Proprietary Name (USAN): Scopolamine Transdermal Therapeutic System

9. LEGAL BASIS FOR SUBMISSION:

This Abbreviated New Drug Application (ANDA) is based upon the reference listed drug (RLD) Transderm Scop®, NDA No. 17-874, manufactured by Novartis. They have indicated that to their knowledge, there are no unexpired patents or exclusivities.

10. PHARMACOL. CATEGORY: Anti-emetic

11. DOSAGE FORM: Film, extended release

12. STRENGTH/POTENCY: 1 mg/3 days

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

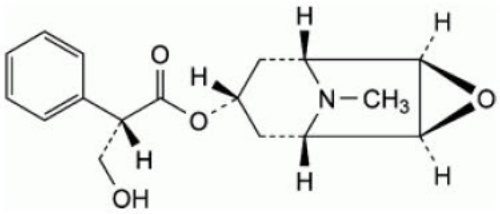
_____ SPOTS product – Form Completed

__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): (-)-a-(hydroxymethyl)-benzeneacetic acid 9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl ester

Chemical Structure:



Molecular Formula: $C_{17}H_{21}NO_4$

Molecular Weight: 303.4

17. RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate/IR	09/11/2014	D. Skanchy
	III			3	Adequate	7/18/07	
	III			3	Adequate	7/18/07	
	III			3	Adequate	3/26/08	
	III			4	NA		
	III			4	NA		
	III			4	NA		

A. DMFs:

[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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending	15-Jul-2014	
Methods Validation	N/A		
Labeling	Minor deficiency	04/29/2014	C. Park
Bioequivalence	Acceptable	1/16/09	Z. Zhao
EA	Categorical Exclusion requested 21 CFR 25.31(a)		
Radiopharmaceutical	N/A		
Clinical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes _____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78830

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC is adequate.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

(b) (4)

[redacted]

II. Summary of Chemistry Assessments

MDD=1.31 mg: ICH Q3b(R2) IT=0.5%; QT=1.0%

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance is not compendial. It is a well known belladonna alkaloid, white to off white crystalline powder that is freely soluble in ethanol and soluble in water. It is the S-enantiomer with a melting point of 66-70 °C and a pKa of 7.55-7.81.

The drug product is non-compendial. This product is a film 0.2 mm thick and 2.5 cm^2, with four layers. Proceeding from the visible surface towards the surface attached to the skin, these layers are: (1) a backing layer of tan-colored, aluminized, polyester film; (2) a drug reservoir of scopolamine, crospovidone, isopropyl palmitate, light mineral oil, and polyisobutylene; (3) a microporous ethylene vinyl acetate copolymer membrane that controls the rate of delivery from the system to the skin surface; and (4) an adhesive formulation of crospovidone, isopropyl palmitate, light mineral oil, polyisobutylene, and scopolamine. A protective peel strip of siliconized polyester, which covers the adhesive layer, is removed before the system is used. The inactive components, crospovidone, isopropyl palmitate, light mineral oil and polyisobutylene, are not released from the system.

It is manufactured by (b) (4)

[redacted]

B. Description of How the Drug Product is Intended to be Used

The Scopolamine Transdermal Therapeutic system is a tan-colored circular patch, 2.5 cm^2, on a clear, oversized, (b) (4) peel strip, which is removed prior to use. To prevent the nausea and vomiting associated with motion sickness, one patch (b) (4) to deliver approximately 1.0 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. To prevent post operative nausea and vomiting, the patch should be applied the evening before scheduled surgery.

C. Basis for Approvability or Not-Approval Recommendation

CMC is adequate.

II. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT- None

ANDA: 078830

APPLICANT: Perrigo R&D Company

DRUG PRODUCT: Scopolamine Transdermal Therapeutic System, 1 mg/3 days.

CMC is adequate.

ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Guohua Li, 07/25/2014
Chemistry Team Leader Name/Date: Dhaval K. Gaglani/ 07/15/14, 07/25/14, 8/24/14
Chemistry Supervisor/Date: Bhagwant Rege/ 07/31/2014, 08/04/2014, 08/26/2014
Project Manager Name/Date: Brijet Burton Coachman, 9-19-2014

TYPE OF LETTER:

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

/s/

GUOHUA LI
09/22/2014

BRIJET N BURTON COACHMAN
09/22/2014

DHAVAL GAGLANI
09/22/2014

BHAGWANT D REGE
09/22/2014

ANDA 78830

Scopolamine Transdermal Therapeutic System 1 mg/72 h

Perrigo Company

Shahnaz Read
Chemistry Division II

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Chemistry Assessment **9**

Chemistry Review Data Sheet

1. ANDA 78830

2. REVIEW #: 4

3. REVIEW DATE: September 19, 2012, revised March 29, 2013

4. REVIEWER: Shahnaz Read

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	February 23, 2007
Amendment	May 11, 2007
Review #1	July 20, 2007
Minor Amendment	January 4, 2008
Review #2	April 4, 2008
Minor Amendments	April 16 and 17, 2012 June 7, 2012
Review #3	July 2, 2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	August 13&14, 2012
Unsolicited Amendment	March 19, 2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Perrigo Company
Address:	515 Eastern Avenue Allegan, MI 49010
Contact:	Diane L. Morgan
Telephone:	269-686-1729
Fax:	269-673-7655

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA

b) Non-Proprietary Name (USAN): Scopolamine Transdermal Therapeutic System

9. LEGAL BASIS FOR SUBMISSION:

This Abbreviated New Drug Application (ANDA) is based upon the reference listed drug (RLD) Transderm Scop®, NDA No. 17-874, manufactured by Novartis. They have indicated that to their knowledge, there are no unexpired patents or exclusivities.

10. PHARMACOL. CATEGORY: Anti-emetic

11. DOSAGE FORM: Transdermal System

12. STRENGTH/POTENCY: 1 mg/72 h

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

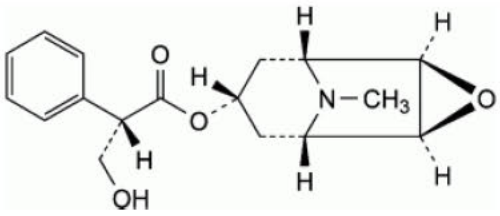
_____ SPOTS product – Form Completed

__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): (-)-a-(hydroxymethyl)-benzeneacetic acid 9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl ester

Chemical Structure:



Molecular Formula: $C_{17}H_{21}NO_4$

Molecular Weight: 303.4

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DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	9/19/12	
	III			1	Adequate	7/18/07	
	III			1	Adequate	7/18/07	
	III			1	Adequate	3/26/08	
	III			4	NA		
	III			4	NA		
	III			4	NA		

[1] Action codes for DMF Table:
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Other codes indicate why the DMF was not reviewed, as follows:
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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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending	3/25/13	
Methods Validation	NA		
Labeling	Acceptable	8/21/12	C. Park
Bioequivalence	Acceptable	1/16/09	Z. Zhao
EA	Categorical Exclusion requested 21 CFR 25.31(a)		
Radiopharmaceutical	NA		
Clinical	Pending		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes _____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78830

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable for CMC.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

(b) (4)

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance is not compendial. It is a well known belladonna alkaloid, white to off white crystalline powder that is freely soluble in ethanol and soluble in water. It is the S-enantiomer with a melting point of 66-70 °C and a pKa of 7.55-7.81.

The drug product is non-compendial. This product is a film 0.2 mm thick and 2.5 cm^2, with four layers. Proceeding from the visible surface towards the surface attached to the skin, these layers are: (1) a backing layer of tan-colored, aluminized, polyester film; (2) a drug reservoir of scopolamine, crospovidone, isopropyl palmitate, light mineral oil, and polyisobutylene; (3) a microporous ethylene vinyl acetate copolymer membrane that controls the rate of delivery from the system to the skin surface; and (4) an adhesive formulation of crospovidone, isopropyl palmitate, light mineral oil, polyisobutylene, and scopolamine. A protective peel strip of siliconized polyester, which covers the adhesive layer, is removed before the system is used. The inactive components, crospovidone, isopropyl palmitate, light mineral oil and polyisobutylene, are not released from the system.

It is manufactured by (b) (4)

B. Description of How the Drug Product is Intended to be Used

The Scopolamine Transdermal Therapeutic system is a tan-colored circular patch, 2.5 cm^2, on a clear, oversized, (b) (4) peel strip, which is removed prior to use. To

prevent the nausea and vomiting associated with motion sickness, one patch (b) (4) to deliver approximately 1.0 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. To prevent post operative nausea and vomiting, the patch should be applied the evening before scheduled surgery.

C. Basis for Approvability or Not-Approval Recommendation

All CMC issues have been resolved.

II. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 078830

APPLICANT: Perrigo Company

DRUG PRODUCT: Scopolamine Transdermal Therapeutic System, 1 mg/72 h.

A. The deficiencies presented below represent MINOR deficiencies.

1. [redacted] (b) (4)

2. The Agency requires evidence that the formulation of a generic product is not less safe than the RLD. We acknowledge that it is possible that different transdermal formulations of the same drug may have different responses to "in-use conditions". To ensure that the RLD labeling with respect to swimming/showering is applicable to the ANDA product, please provide information about the formulation performance to ensure that the sensitivity to in-use conditions like water/hot water exposure of the generic product is not more pronounced than that of the RLD. You may design and provide an in vitro study (e.g., skin flux permeation study with "stressed" conditions to mimic certain in-use conditions) to compare in vitro release data to the RLD at normal and "stress" situations: If the generic product was not more sensitive than the RLD, it would be acceptable. Such in vitro data would assure that the proposed generic TDDS product would not create a greater risk when exposed to in-use conditions than the RLD. Please refer to the FDA response to the CP 2012-P-0932 (see link below) for additional information.
http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0932-0003

3 [redacted] (b) (4)

Sincerely yours,

{See appended electronic signature page}

Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 78830
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/3/29/13

HFD-645/SRosencrance/

HFD-640/BCai/

HFD-617/FNice/

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

/s/

SHAHNAZ T READ
03/29/2013

FRANK J NICE
03/29/2013

SUSAN M ROSENCRANCE
04/04/2013

BING CAI
04/05/2013

ANDA 78830

Scopolamine Transdermal Therapeutic System 1 mg/72 h

Perrigo Company

Shahnaz Read
Chemistry Division II

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B. Description of How the Drug Product is Intended to be Used 7

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Chemistry Assessment **9**

Chemistry Review Data Sheet

1. ANDA 78-830

2. REVIEW #: 3

3. REVIEW DATE: July 2, 2012

4. REVIEWER: Shahnaz Read

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	February 23, 2007
Amendment	May 11, 2007
Review #1	July 20, 2007
Minor Amendment	January 4, 2008
Review #2	April 4, 2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendments	April 16 and 17, 2012 June 7, 2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Perrigo Company
Address:	515 Eastern Avenue Allegan, MI 49010
Contact:	Diane L. Morgan
Telephone:	269-686-1729
Fax:	269-673-7655

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Scopolamine Transdermal Therapeutic System

9. LEGAL BASIS FOR SUBMISSION:

This Abbreviated New Drug Application (ANDA) is based upon the reference listed drug (RLD) Transderm Scop®, NDA No. 17-874, manufactured by Novartis. They have indicated that to their knowledge, there are no unexpired patents or exclusivities.

10. PHARMACOL. CATEGORY: Anti-emetic

11. DOSAGE FORM: Transdermal System

12. STRENGTH/POTENCY: 1 mg/72 h

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

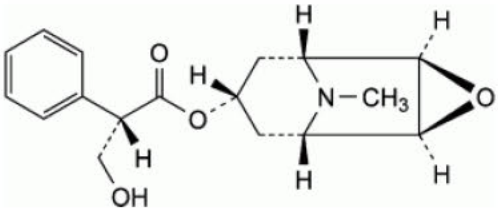
_____ SPOTS product – Form Completed

__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): (-)-a-(hydroxymethyl)-benzeneacetic acid 9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl ester

Chemical Structure:



Molecular Formula: $C_{17}H_{21}NO_4$

Molecular Weight: 303.4

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Inadequate	6/15/12	DMF holder has been notified
	III			1	Adequate	7/18/07	
	III			1	Adequate	7/18/07	
	III			1	Adequate	3/26/08	
	III			4	NA		
	III			4	NA		
	III			4	NA		

[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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending	7/9/12	
Methods Validation	NA		
Labeling	Pending		
Bioequivalence	Pending		
EA	Categorical Exclusion requested 21 CFR 25.31(a)		
Radiopharmaceutical	NA		
Clinical	Pending		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes _____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78830

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable for CMC.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

(b) (4)

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance is not compendial. It is a well known belladonna alkaloid, white to off white crystalline powder that is freely soluble in ethanol and soluble in water. It is the S-enantiomer with a melting point of 66-70 °C and a pKa of 7.55-7.81.

The drug product is non-compendial. This product is a film 0.2 mm thick and 2.5 cm^2, with four layers. Proceeding from the visible surface towards the surface attached to the skin, these layers are: (1) a backing layer of tan-colored, aluminized, polyester film; (2) a drug reservoir of scopolamine, crospovidone, isopropyl palmitate, light mineral oil, and polyisobutylene; (3) a microporous ethylene vinyl acetate copolymer membrane that controls the rate of delivery of from the system to the skin surface; and (4) an adhesive formulation of crospovidone, isopropyl palmitate, light mineral oil, polyisobutylene, and scopolamine. A protective peel strip of siliconized polyester, which covers the adhesive layer, is removed before the system is used. The inactive components, crospovidone, isopropyl palmitate, light mineral oil and polyisobutylene, are not released from the system.

It is manufactured by (b) (4)

B. Description of How the Drug Product is Intended to be Used

The Scopolamine Transdermal Therapeutic system is a tan-colored circular patch, 2.5 cm^2, on a clear, oversized, hexagonal peel strip, which is removed prior to use. To

prevent the nausea and vomiting associated with motion sickness, one patch (b) (4) to deliver approximately 1.0 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. To prevent post operative nausea and vomiting, the patch should be applied the evening before scheduled surgery.

C. Basis for Approvability or Not-Approval Recommendation

Firm has been asked for more information on the (b) (4)

II. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 078830

APPLICANT: Perrigo Company

DRUG PRODUCT: Scopolamine Transdermal Therapeutic System, 1 mg/72 h.

A. The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)
2.
3.
4.
5.
6.
7.

(b) (4)

B. Please note and acknowledge the following:

1. (b) (4)

2.

Sincerely yours,

{See appended electronic signature page}

Glen J. Smith
Director
Division of Chemistry 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/

SHAHNAZ T READ
07/11/2012

FRANK J NICE
07/11/2012

SUSAN M ROSENCRANCE
07/11/2012

ANDA 78-830

Scopolamine Transdermal Therapeutic System 1 mg/72 h

Perrigo Company

Shahnaz Read
Chemistry Division II

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Chemistry Assessment **9**

Chemistry Review Data Sheet

1. ANDA 78-830

2. REVIEW #: 2

3. REVIEW DATE: April 4, 2008

4. REVIEWER: Shahnaz Read

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	February 23, 2007
Amendment	May 11, 2007
Review #1	July 20, 2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	January 4, 2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Perrigo Company
Address:	515 Eastern Avenue Allegan, MI 49010
Contact:	Diane L. Morgan
Telephone:	269-686-1729
Fax:	269-673-7655

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Scopolamine Transdermal Therapeutic System

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION:

This Abbreviated New Drug Application (ANDA) is based upon the reference listed drug (RLD) Transderm Scop®, NDA No. 17-874, manufactured by Novartis. They have indicated that to their knowledge, there are no unexpired patents or exclusivities.

10. PHARMACOL. CATEGORY: Anti-emetic

11. DOSAGE FORM: Transdermal System

12. STRENGTH/POTENCY: 1 mg/72 h

13. ROUTE OF ADMINISTRATION: Transdermal

14. Rx/OTC DISPENSED: __X__ Rx ____ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

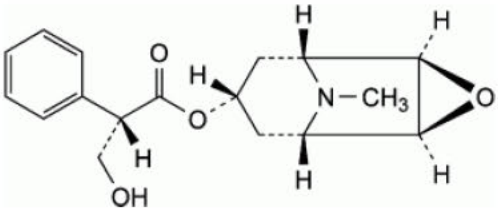
_____ SPOTS product – Form Completed

__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): (-)-a-(hydroxymethyl)-benzeneacetic acid 9-methyl-3-oxa-9-azatricyclo[3.3.1.$0^{2,4}$]non-7-yl ester

Chemical Structure:



Molecular Formula: $C_{17}H_{21}NO_4$

Molecular Weight: 303.4

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Inadequate	3/19/08	DMF holder has been notified
	III			1	Adequate	7/18/07	
	III			1	Adequate	7/18/07	
	III			1	Adequate	3/26/08	
	III			4	NA		
	III			4	NA		
	III			4	NA		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
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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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	6/26/07	
Methods Validation	NA		
Labeling	Pending		
Bioequivalence	Pending		
EA	Categorical Exclusion requested 21 CFR 25.31(a)		
Radiopharmaceutical	NA		
Clinical	Pending		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes _____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-830

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable for CMC.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance is not compendial. It is a well known belladonna alkaloid, white to off white crystalline powder that is freely soluble in ethanol and soluble in water. It is the S-enantiomer with a melting point of 66-70 °C and a pKa of 7.55-7.81.

The drug product is non-compendial. This product is a film 0.2 mm thick and 2.5 cm^2, with four layers. Proceeding from the visible surface towards the surface attached to the skin, these layers are: (1) a backing layer of tan-colored, aluminized, polyester film; (2) a drug reservoir of scopolamine, crospovidone, isopropyl palmitate, light mineral oil, and polyisobutylene; (3) a microporous ethylene vinyl acetate copolymer membrane that controls the rate of delivery of from the system to the skin surface; and (4) an adhesive formulation of crospovidone, isopropyl palmitate, light mineral oil, polyisobutylene, and scopolamine. A protective peel strip of siliconized polyester, which covers the adhesive layer, is removed before the system is used. The inactive components, crospovidone, isopropyl palmitate, light mineral oil and polyisobutylene, are not released from the system.

It is manufactured by [redacted] (b) (4)

B. Description of How the Drug Product is Intended to be Used

The Scopolamine Transdermal Therapeutic system is a tan-colored circular patch, 2.5 cm^2, on a clear, oversized, [redacted] (b) (4) peel strip, which is removed prior to use. To prevent the nausea and vomiting associated with motion sickness, one patch [redacted] (b) (4) to deliver approximately 1.0 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is

required. To prevent post operative nausea and vomiting, the patch should be applied the evening before scheduled surgery.

C. Basis for Approvability or Not-Approval Recommendation

Firm needs to resolve issues (b) (4).

Following this page, 26 Pages Withheld in Full as (b)(4)

II. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-830 APPLICANT: Perrigo Company

DRUG PRODUCT: Scopolamine Transdermal Therapeutic System, 1 mg/72 h.

A. The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)

2.

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 78-830
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/4/4/08

HFD-645/DMaldonado/4/6/08

HFD-617/TLiu/4/7/08

TYPE OF LETTER: MINOR

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

/s/

Shanaz Read
4/7/2008 03:56:52 PM
CHEMIST

Theresa Liu
4/8/2008 10:46:10 AM
CSO

Damaris Maldonado
4/8/2008 11:33:14 AM
CHEMIST

ANDA 78-830

Scopolamine Transdermal Therapeutic System 1 mg/72 h

Perrigo Company

Shahnaz Read
Chemistry Division II

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Chemistry Assessment **9**

Chemistry Review Data Sheet

1. ANDA 78-830

2. REVIEW #: 1

3. REVIEW DATE: July 20. 2007

4. REVIEWER: Shahnaz Read

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	February 23, 2007
Amendment	May 11, 2007

7. NAME & ADDRESS OF APPLICANT:

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Address:	515 Eastern Avenue Allegan, MI 49010
Contact:	Diane L. Morgan
Telephone:	269-686-1729
Fax:	269-673-7655

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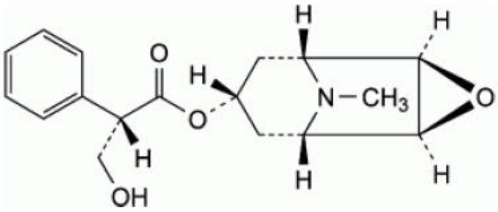
Chemical Structure:



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Molecular Weight: 303.4

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(b) (4)	II		(b) (4)	1	Inadequate	7/18/07	DMF holder has been notified
	III			1	Adequate	7/18/07	
	III			1	Adequate	7/18/07	
	III			6	DMF is inactive		Applicant informed
	III			4	NA		

[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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NA		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending		
Methods Validation	NA		
Labeling	Pending		
Bioequivalence	Pending		
EA	Categorical Exclusion requested 21 CFR 25.31(a)		
Radiopharmaceutical	NA		
Clinical	Pending		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes _____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-830

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable for CMC.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug substance is not compendial. It is a well known belladonna alkaloid, white to off white crystalline powder that is freely soluble in ethanol and soluble in water. It is the S-enantiomer with a melting point of 66-70 °C and a pKa of 7.55-7.81.

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It is manufactured by [redacted] (b) (4)

B. Description of How the Drug Product is Intended to be Used

The Scopolamine Transdermal Therapeutic system is a tan-colored circular patch, 2.5 cm^2, on a clear, oversized, [redacted] (b) (4) peel strip, which is removed prior to use. To prevent the nausea and vomiting associated with motion sickness, one patch [redacted] (b) (4) to deliver approximately 1.0 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is

required. To prevent post operative nausea and vomiting, the patch should be applied the evening before scheduled surgery.

C. Basis for Approvability or Not-Approval Recommendation

Firm needs to resolve issues (b) (4) (b) (4) as noted in the deficiency letter.

Following this page, 23 Pages Withheld in Full as (b)(4)

II. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-830 APPLICANT: Perrigo Company

DRUG PRODUCT: Scopolamine Transdermal Therapeutic System, 1 mg/72 h.

A. The deficiencies presented below represent MINOR deficiencies.

(b) (4)

1.

2.

3.

4.

5.

6.

7.

8.

9.

10.

11.

12. (b) (4)

13.

B. Comments:

1. The labeling and bioequivalence portions of your application are under review. Deficiencies, if any, will be conveyed to you under separate cover.

2. Please provide updated stability data for the exhibit batch.

3. Please provide representative samples of your product and the RLD to assist in our evaluation of the ANDA. The samples should be sent separately to:

   Theresa Liu, Project Manager, Team 7
   Division of Chemistry II
   Office of Generic Drugs
   7500 Standish Place
   Rockville, MD 20855

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 78-830
DIV FILE
Field Copy

Endorsements:

HFD-645/SRead/7/20/07

HFD-645/SFurness/8/7/07

HFD-617/TLiu/8/7/07

TYPE OF LETTER: MINOR

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

/s/

Shanaz Read
9/26/2007 02:49:14 PM
CHEMIST

Theresa Liu
9/27/2007 09:47:28 AM
CSO

Michael S Furness
9/27/2007 11:33:05 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78830

STATISTICAL REVIEWS

ANDA 078830 ADDENDUM TO THE STATISTICAL REVIEW

Comments on the additional adhesion study 12/22/2014

The sponsor explored two statistical approaches and concluded that the test product is non-inferior to the reference for adhesion. These approaches are discussed in this addendum to the statistical review in the sections below. Information is taken from the FDA's statistical report (parts in italic were copied from sponsor's report) except the last table.

1. A non-parametric analysis to compare the median of test versus reference using bootstrap approach.

"As the CAS were shown not to be normally distributed, a non-parametric method was

used for treatment comparison.

For non-parametric analysis, the appropriate hypotheses are:

H0: Median (T - 1.25R) > 0 (not non-inferior)

H1: Median (T - 1.25R) ≤ 0 (non-inferior)

The Bootstrap approach was used to test the significance in hypothesis testing.

The upper bound for the 95% one-sided confidence interval was equal to zero (0). Therefore, the adhesion of the test patch was considered to be non-inferior to that of the reference patch."

To demonstrate the FDA's concern with the use of the bootstrap approach in this ANDA, we first present a frequency table from our statistical review.

Frequency of mean cumulative adhesion scores (N=77)

	0	0.17	0.33	0.5	0.67	0.83	1	1.17	1.33	1.67	1.83	2	2.17	2.67	3.33	4
Test	52	2	1	3	6	6	2	1	1	1	1		1			
Reference	56	2	2	3	4	3			2			1		2	1	1

From the above frequency table, it is clear that more than half of the subjects have adhesion scores of zero at all time points, 67.5% (52/77) for test patch and 72.7% (56/77) for reference patch. As a result, it is likely that the median of adhesion scores will always be zero in a bootstrap sample. If the statistical test were to be based on a bootstrap analysis, and non-inferiority concluded, then we have accepted, in effect, a "50/90 rule". It roughly means that a

non-inferiority test could be passed as long as half (or just over half) of the subjects have 90% adhesion (score=0) for test and reference patch. It seems too loose of a criterion based on our statistical view. Of course, the final decision will be made based on clinical judgment.

2. A binary analysis of the proportion of patches that completely detached

The number and proportion of patches that completely detached are presented in Table 2.3.

Table 2.3 Proportion of Patches that Completely Detached (PPPA)

		Adhesion Score	
Product*	**N**	**≤ 3 (not detached) N (%)**	**4 (detached) N (%)**
A	77	76 (98.70)	1 (1.30)
B	77	70 (90.91)	7 (9.09)

*A = Scopolamine Transdermal Delivery System, 2.5 cm^2, label claim 1.31 mg/unit (Manufactured by AVĒVA Drug Delivery Systems, an Apotex Company; Distributed by Perrigo)
B = TRANSDERM-SCŌP® (scopolamine) transdermal system, 1.5 mg (Manufactured by ALZA Corporation; Distributed by Novartis Consumer Health, Inc.)

In the FDA's statistical review, many possible binary endpoints were considered. In addition to the primary endpoint analyses, analyses for the secondary endpoints were conducted to compare the test and reference with regard to the proportion of subjects who had mean and individual visit adhesion scores greater than 0, 1, 2, and 3.

Based on the 95% upper confidence bound for the difference in proportions for mean and by-visit scores, the test might exceed the reference by at most 18.2 and 23.9 percentage points with regard to the proportion of subjects who had mean and visit at hour 48 adhesion scores greater than 0, i.e., partial detachment.

Moreover, considering the difference in proportions for mean and by-visit scores, the test might exceed the reference by at most 1.7 and 2.1 percentage points with regard to the proportion of subjects who had mean and visit at hour 12 adhesion scores greater than 3, i.e., full detachment.

In Table 5 in the statistical review, shown below, these results as well as the corresponding values for other cut points, that is, other possible defining values of 'insufficiently attached' or, 'detachment' are given. The counts of discordant pairs are also given in Table 5; see footnotes to that table.

We think it is a clinical policy decision as to what dichotomization should be used in determining non-inferiority of the test product with regard to adhesion. The sponsor, in the analyses submitted with this ANDA, takes only full detachment, score =4, to be 'insufficiently attached.'

Analysis of the dichotomized adhesion score for score>crit versus others (N=77)*

Crit	0			1			2			3		
	b	c	UB	b	C	UB	b	c	UB	b	c	UB
Mean	17	13	**0.182**	4	6	0.054	1	4	0.021	0	2	0.017
Visit (Hour)												
12	4	1	0.099	0	1	0.021	0	1	0.021	0	1	0.021
24	8	5	0.129	0	2	0.017	0	2	0.017	0	2	0.017
36	16	7	0.230	1	4	0.021	0	4	0.003	0	4	0.003
48	18	9	**0.239**	3	4	0.056	1	5	0.012	1	5	0.012
60	17	12	0.192	4	8	0.034	2	7	0.011	1	7	-0.006
72	17	12	0.192	6	8	0.067	3	7	0.028	1	7	-0.006

*: Critical value (crit) was used to dichotomize the score.

b = number of subjects with a negative outcome (detachment, score>crit) using the test but not the reference;

c = number of subjects with a negative outcome (detachment, score>crit) using the reference but not the test.

UB (95% Upper Bound) for $P_T - P_R$ = P (mean cumulative/visit adhesion score greater than crit for test) - P (mean cumulative/visit adhesion score greater than crit for reference).

3. Distributions of the adhesion scores in the original and additional study

Additional information to be considered in evaluating the adhesion data for ANDA 078830 is given below:

A. Frequency tables

Shown below are two adhesion score frequency tables from ANDA 078830 (original and additional adhesion study).

Frequency of adhesion scores (N=29, original study)

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 (b) (6) reference patch fell off after Hour 48. A score of 4 at Hour 48 was carried forward to Hour 60 and 72.

Frequency of adhesion scores (N=77 additional adhesion study)

Evaluation hours	Treatment	Adhesion score				
		0	1	2	3	4
12	Test	73	4			
	Reference	76				1
24	Test	68	9			
	Reference	71	4			2
36	Test	59	17	1		
	Reference	68	5			4
48	Test	55	17	4		1
	Reference	64	7	1		5
60	Test	54	18	3	1	1
	Reference	59	9	2		7
72	Test	52	18	4	2	1
	Reference	57	11	2		7

Frequency of mean adhesion scores (N=29, original study)

Mean	0	0.167	0.333	0.5	0.667	0.8333	1	1.667	2	2.167	2.667
Test	3	6	11	3	2	1		1	1	1	
Reference	2	7	9	3	3	3	2				1

Frequency of mean adhesion scores (N=77, additional study)

Mean	0	0.17	0.33	0.5	0.67	0.83	1	1.17	1.33	1.67	1.83	2	2.17	2.67	3.33	4
Test	52	2	1	3	6	6	2	1	1	1	1		1			
Reference	56	2	2	3	4	3			2			1		2	1	1

(1) The proportions of the subjects who had mean adhesion score equal to zero (at least 90% attached): 67.5% (52/77) for test patch and 72.7% (56/77) for reference patch in the additional study. 10.3% (3/29) for test patch and 6.9% (2/29) for reference patch in the original study.

(2) The proportions of the subjects who had mean adhesion score less than or equal to 1 (at least 75% attached): 93.5% (72/77) for test patch and 90.9% (70/77) for reference patch in the additional study. 89.7% (26/29) for test patch and 96.6% (28/29) for reference patch in the original study.

B. High variation in the data from the additional adhesion study

Analysis for the mean cumulative adhesion scores using mixed model

Study	Sample size	Test		Reference		Upper limit one-sided 95%CB (test-1.25ref)	Pass the Non-inferiority test
		mean(standard deviation)	CV	mean(standard deviation)	CV		
Original	29	0.4711 (0.5119)	109	0.4944 (0.4961)	100	0.1059	No
Additional	77	0.2771 (0.4841)	174	0.3247 (0.7751)	239	0.068	No

The coefficient of variation (CV), which is defined as 100 times the standard deviation divided by the mean, is a good way to express the variation in the data. The additional adhesion study has high CV for both test (174) and reference (239), which are much higher than the original study, where test CV =109 and reference CV =100. This higher variation makes the Upper limit of the one-sided 95% CB (test-1.25Ref.) higher, leading to failure of the non-inferiority test using mixed model analysis. Regardless of the variability, the mean of test (0.2771) is less than reference (0.3247) in the additional adhesion study.

The reference patch in the additional study has much higher variation than the test patch in both studies and the reference patch in original study.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ANDA/Serial Number:	078830 (Study No. 11325301)
Drug Name:	Scopolamine Transdermal System, 1.31 mg
Indication(s):	Motion sickness and recovery from anesthesia and surgery
Reference Listed Drug:	Transderm Scop® (Novartis) 1.5mg
Applicant:	Perrigo R & D Company.
Date(s):	Submitted March 14, 2014
Biometrics Division:	DB6
Statistical Reviewer:	Huaixiang Li, Ph.D.
Concurring Reviewers:	Stella C Grosser, Ph.D.
Medical Division:	Division of Clinical Review (DCR) in OGD
Clinical Team:	Sunny Tse, Ph.D.
Keywords:	adhesion, non-inferiority, mixed model, matched pair analysis

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1 EXECUTIVE SUMMARY

1.1 Conclusions and recommendations

The primary analysis of mean scores failed to show that the test patch was non-inferior to the reference patch for adhesion based on the results from the mixed linear model.

1.2 Brief overview of clinical studies

This review is for an additional adhesion study (No. 11325301) submitted to FDA dated March 14, 2014.

ANDA 078830 was submitted to FDA on February 23, 2007 which included two studies: a two-period irritation and sensitization study of the test system, using the test placebo patch (Protocol PRG-603); and a pharmacokinetic study that additionally evaluated adhesion of the test system, using the active test patch (Protocol PRG-604).

FDA sent out a deficiencies letter on May 31, 2013 which contained the comments: "***In the pharmacokinetic/adhesion study (PRG-604), your product was statistically significantly less adhesive than the reference product. The study failed to show noninferiority of your Scopolamine Extended-release Transdermal Film to the reference product with regard to adhesion performance.***"

Perrigo acknowledged Agency's comment and conducted a standalone adhesion study (No. 11325301) in order to generate adequate data to ensure that the adhesive performance of Perrigo's Scopolamine Transdermal Delivery System 1.31mg is at least as good as reference product Transderm Scop® 1.5mg.

Study 11325301 was a multiple-center, single-application, randomized, two-treatment, two-period, four-sequence, crossover study comparing the adhesive properties of the test patch, scopolamine transdermal therapeutic system, 1.31 mg (manufactured by AVĒVA Drug Delivery Systems, an Apotex Company; distributed by Perrigo), relative to those of the reference patch, TRANSDERM-SCŌP® (scopolamine) transdermal therapeutic system, 1.5 mg (manufactured by ALZA Corporation; distributed by Novartis Consumer Health, Inc.).

1.3 Statistical issues and findings

I) The mean cumulative adhesion scores were analyzed using a mixed linear model. The one-sided 95% upper CB for the adjusted mean difference ($\mu_T - 1.25\mu_R$) was greater than zero (0.068) and the non-inferiority test was failed for test versus reference. Hence, the adhesion property of the test product is considered worse than that of the reference product.

II) Based on the 95% upper confidence bound for the difference in proportions for mean and by-visit scores, (1) the test might exceed the reference by at most 18.2 and 23.9 percentage points with regard to the proportion of subjects who had mean and hour-48 visit adhesion scores greater

than 0; (2) the test might exceed the reference by at most 1.7 and 2.1 percentage points with regard to the proportion of subjects who had mean and 12 hour visit adhesion scores greater than 3 (full detachment).

2 INTRODUCTION

2.1 Overview

The Transderm Scop® (scopolamine extended-release transdermal film) system is a circular flat patch containing 1.5 mg of scopolamine base and designed to deliver approximately 1.0 mg of scopolamine over 3 days. It is indicated in adults for prevention of nausea and vomiting associated with motion sickness and recovery from anesthesia and surgery. The patch is to be applied only to skin in the post auricular area. Only one patch should be worn at any time, and the patch, which has a reservoir design, is not to be cut. One patch is to be applied for up to 72 hours and it can be replaced if necessary.

The data were submitted electronically. The data files are located in the following directory:

\\cdsesub1\evsprod\anda078830**0012**\m5\datasets**11325301**\listings

In this report, all tables, unless otherwise specified, are taken from FDA clinical reviewer's or the sponsor's report. Analysis results and tables calculated by FDA statistical reviewer are noted as such in the text and/or the title of the tables.

3 STATISTICAL EVALUATION

3.1 Statistical methodologies

The statistical methods used in analysis are described in this section.

In the study, each subject received two patches: test patch in one period and reference patch in another period, with sequence randomized. As a result, observations taken from the same subject might be correlated. For the analysis of continuous data, linear mixed models were used in the comparison of means; the random effects in the mixed model structure assessed and reflected the correlation of observations. For matched dichotomized pairs data, the McNemar test was used to compare the test and the comparator in the difference between 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 adhesion score.

The statistical method for continuous data uses the estimate of the adjusted mean difference $\mu_T - 1.25\mu_C$, to test the hypotheses

H_0: $\mu_T - 1.25\mu_C > 0$ vs H_1: $\mu_T - 1.25\mu_C \leq 0$

where μ_T is the mean response for the test and μ_C is the mean response for the comparator. One-sided 95% confidence intervals (CIs) were obtained based on the estimated means. If the upper limit of the CI is less than or equal to 0, the null hypothesis is rejected and the test patch may be considered non-inferior to the comparator. Otherwise it is concluded that the test may be worse than the comparator. The comparator is the reference patch in this study.

The SAS® (Version 9.2) 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*Comparator' 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 adhesion score, and adhesion score per evaluation hour. The method based on the work of McNemar was used to compare the test and comparator with regard to the binary endpoints (proportions).

For the method used to assess the non-inferiority of the test versus comparator, a 95% upper confidence bound for the difference of the proportions between test and comparator was calculated.

Let
p_T = rate of the test, p_C = rate of the comparator (p_T and p_C were adhesion rates in this analysis);
n = total number of subjects;
b = number of subjects with a negative outcome (detachment) using the test but not the comparator;
and c = number of subjects with a negative outcome (detachment) using the comparator but not the test.
Hypotheses: H_0: $p_T - p_C > \delta$ vs H_1: $p_T - p_C \leq \delta$

Data on two outcomes from matched pairs

		Test	
		Score<=crit	Score> crit
Comparator	Score<=crit	a	b
	Score> crit	c	d
Total n=a+b+c+d			

*: Critical value (crit) was used to dichotomize the score.

The difference of p_T - p_C may be estimated by the quantity (b – c)/n.

Based on McNemar's test, the 95% upper confidence bound (U) for the quantity p_T - p_C was calculated as

$$U = \frac{(b-c)}{n} + \frac{1}{n} + 1.645 \frac{\sqrt{(b+c) - \frac{(b-c)^2}{n}}}{n}$$

This formula for the upper confidence bound is algebraically the same as that given by Fleiss (1981, p117).

For any given non-inferiority bound δ, the null hypothesis H_0 may be rejected if this 95% upper confidence bound U for the quantity p_T - p_C is less than or equal to δ, that is: $U \leq \delta$. Rejection of the null hypothesis H_0 supports the conclusion of non-inferiority of the test to the comparator. The non-inferiority standard δ is yet to be decided by OGD.

3.2 Study No. 11325301: Evaluation of adhesion

3.2.1 Study design and endpoints

Study Objective

The primary objective was to compare the adhesive properties of a test scopolamine transdermal therapeutic system, 1.31 mg (Perrigo) relative to those of the marketed reference formulation, TRANSDERM-SCŌP® in healthy adult subjects.

Study design

This was a multiple-center, single-application, randomized, two-treatment, two-period, four-sequence, crossover study comparing the adhesive properties of the test and reference patch.

Subjects had one (1) scopolamine transdermal therapeutic system applied behind the ear (postauricular area) and kept in place for approximately 72 hours in each period of the study. Subjects received the test product in one of the study periods and the reference product in the other study period according to the randomization schedule. As the primary objective of this study was to compare adhesion, there was no washout period between the study periods.

Immediately after application (0 hour) and at 12, 24, 36, 48, 60, and 72 hours (before patch removal) after application (±60 minutes) the patches were checked for the degree of adhesion by a trained scorer using the FDA-recommended rating scale.

The study was conducted with 80 (71 completing, 77 included in PPPA) healthy adult subjects in accordance with Protocol No. PRG-NY-14-007 (Revision 1).

Treatments

Treatment	Description
Product A (Test)	Scopolamine transdermal therapeutic system, 1.31 mg (manufactured by AVĒVA Drug Delivery Systems, an Apotex Company; distributed by Perrigo),
Product B (Reference)	TRANSDERM-SCŌP® (scopolamine) Transdermal therapeutic system, 1.5 mg (manufactured by ALZA Corporation; distributed by Novartis Consumer Health, Inc.)

Adhesion evaluations

0 =	≥90% 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=	>0% to <50% adhered, but not detached (more than half the system lifting off of the skin without falling off)
4 =	0% adhered - patch detached (patch completely off the skin)

Clinical endpoints

Primary endpoint: Mean Cumulative Adhesion Scores

The mean cumulative adhesion scores were obtained by adding total observations at 12, 24, 36, 48, 60, and 72 hours in the application period and dividing by the number of observations (6).

Secondary endpoints: The clinical reviewer requested a comparison of test versus reference with regard to the proportion of patch applications with meaningful detachment. The analyses were conducted to compare the test and reference with regard to the proportion of subjects who had mean and visit adhesion scores greater than 0, 1, 2, and 3.

3.2.2 Subject disposition

A total of 80 healthy adult subjects were enrolled and 77 subjects were included in the sponsor's Per Protocol (ADHPP) and FDA's Per Protocol (ADHFPP) populations for adhesion analysis.

Three subjects were excluded from the ADHPP/ADHFPP populations.

- Subject (b) (6) did not return as scheduled for the Period I 60 hour adhesion assessment and thus was considered to have voluntarily withdrawn from the study.

- Subject (b) (6) was discontinued by the Investigator following removal of the Period I patch on Day 4 for a protocol deviation for the subject's use of dextroamphetamine sulfate for recreational purposes on Day 3.
- Subject (b) (6) voluntarily withdrew from the study for personal reasons before the Period I 72 hour adhesion assessment.

Eight subjects in the ADHPP/ADHFPP population - (b) (6) (b) (6) - experienced complete detachment of the patch application. Data from these subjects were included in the analyses with a score of 4 (complete patch detachment) carried forward (LOCF) shown below.

		Adhesion score					
Subject	Treatment	12 Hours	24 hours	36 Hours	48 Hours	60 Hours	72 Hours
(b) (6)	Reference	0	0	0	4	4	4
	Reference	0	0	0	0	4	4
	Reference	0	0	4	4	4	4
	Reference	0	0	4	4	4	4
	Test	0	0	1	4	4	4
	Reference	0	0	0	0	4	4
	Reference	0	4	4	4	4	4
	Reference	4	4	4	4	4	4

The demographic characteristics of the ADHFPP population are summarized in Table 1.

Table 1: Demographic characteristics (ADHFPP, N=77)

Age (years)	
Mean (Range)	41.38 (20-64)
Gender	
Female	39 (50.65%)
Male	38 (49.35%)
Race	
White	23 (29.87%)
Black/African American	36 (46.75%)
Others	18 (23.38%)

3.2.3 Results and conclusions

3.2.3.1 Sponsor's analysis results

The sponsor concluded the test patch is non-inferior to the reference patch based on their analysis in their synopsis below.

"The primary endpoint of adhesion was the Cumulative Adhesion Score (CAS) during the 72-hour application period.

The primary objective related to adhesion was whether the level of adhesion of the test patch is no worse than (non-inferior to) that of the reference patch. Because the adhesion scale

shows better adhesion for lower values, the relevant hypotheses for evaluating non-inferiority are:
H0: T - (1.25 x R) > 0 (not non-inferior)
H1: T - (1.25 x R) ≤ 0 (non-inferior)

As the CAS were shown not to be normally distributed, a non-parametric method was used for treatment comparison.
For non-parametric analysis, the appropriate hypotheses are:
H0: Median (T - 1.25R) > 0 (not non-inferior)
H1: Median (T - 1.25R) ≤ 0 (non-inferior)
The Bootstrap approach was used to test the significance in hypothesis testing.

The upper bound for the 95% one-sided confidence interval was equal to zero (0). Therefore, the adhesion of the test patch was considered to be non-inferior to that of the reference patch.

The number and proportion of patches that completely detached are presented in Table 2.3.

Table 2.3 Proportion of Patches that Completely Detached (PPPA)

		Adhesion Score	
Product*	**N**	**≤ 3 (not detached) N (%)**	**4 (detached) N (%)**
A	77	76 (98.70)	1 (1.30)
B	77	70 (90.91)	7 (9.09)

*A = Scopolamine Transdermal Delivery System, 2.5 cm^2, label claim 1.31 mg/unit (Manufactured by AVĒVA Drug Delivery Systems, an Apotex Company; Distributed by Perrigo)
B = TRANSDERM-SCŌP® (scopolamine) transdermal system, 1.5 mg (Manufactured by ALZA Corporation; Distributed by Novartis Consumer Health, Inc.)

CONCLUSION: *The adhesion of the test scopolamine transdermal therapeutic system, 1.31 mg (manufactured by AVĒVA Drug Delivery Systems, an Apotex Company; distributed by Perrigo) was shown to be statistically non-inferior to that of the reference product, TRANSDERM-SCŌP® (scopolamine) transdermal therapeutic system, 1.5 mg (manufactured by ALZA Corporation; distributed by Novartis Consumer Health, Inc.), in the primary non-parametric analysis."*

3.2.3.2 Reviewer's results

The analysis is based on FDA's Per Protocol population (same as the sponsor's PP population) and follows the guidance-recommended approach.

Table 2: Frequency of adhesion scores (N=77)

Evaluation hours	Treatment	Adhesion score				
		0	1	2	3	4
12	Test	73	4			
	Reference	76				1
24	Test	68	9			
	Reference	71	4			2
36	Test	59	17	1		
	Reference	68	5			4
48	Test	55	17	4		1
	Reference	64	7	1		5
60	Test	54	18	3	1	1
	Reference	59	9	2		7
72	Test	52	18	4	2	1
	Reference	57	11	2		7

Primary endpoint: Mean cumulative adhesion score

The frequency of mean cumulative adhesion scores per each patch is shown in Table 3. The mean cumulative adhesion scores were analyzed using a mixed model and are presented in Table 4.

Table 3: Frequency of mean cumulative adhesion scores (N=77)

	0	0.17	0.33	0.5	0.67	0.83	1	1.17	1.33	1.67	1.83	2	2.17	2.67	3.33	4
Test	52	2	1	3	6	6	2	1	1	1	1		1			
Reference	56	2	2	3	4	3			2			1		2	1	1

Table 4: Analysis for the mean cumulative adhesion scores using mixed model (N=77)

	Test (Ls mean)	Reference (Ls mean)	Upper limit one-sided 95%CB (test-1.25ref)	Pass the Non-inferiority test
Mean	0.2771	0.3247	0.068	No

Non-inferiority analyses based on the mean cumulative adhesion scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference (μ_T -1.25μ_R) was larger than zero (0.068) and the non-inferiority test was failed for test versus reference patch. Therefore, the adhesion potential of the test is worse than that of the reference.

Secondary endpoint: Dichotomized adhesion scores

Table 5: Analysis of the dichotomized adhesion score for score>crit versus others (N=77)*

Crit	0			1			2			3		
	b	c	UB	b	c	UB	b	c	UB	b	c	UB
Mean	17	13	**0.182**	4	6	0.054	1	4	0.021	0	2	0.017
Visit (Hour)												
12	4	1	0.099	0	1	0.021	0	1	0.021	0	1	0.021
24	8	5	0.129	0	2	0.017	0	2	0.017	0	2	0.017
36	16	7	0.230	1	4	0.021	0	4	0.003	0	4	0.003
48	18	9	**0.239**	3	4	0.056	1	5	0.012	1	5	0.012
60	17	12	0.192	4	8	0.034	2	7	0.011	1	7	-0.006
72	17	12	0.192	6	8	0.067	3	7	0.028	1	7	-0.006

*: Critical value (crit) was used to dichotomize the score.
b = number of subjects with a negative outcome (detachment, score>crit) using the test but not the reference;
c = number of subjects with a negative outcome (detachment, score>crit) using the reference but not the test.
UB (95% Upper Bound) for $P_T - P_R$ = P (mean cumulative/visit adhesion score greater than crit for test) - P (mean cumulative/visit adhesion score greater than crit for reference).

In addition to the primary endpoint analyses, analyses for the secondary endpoints were conducted to compare the test and reference with regard to the proportion of subjects who had mean and visit adhesion scores greater than 0, 1, 2, and 3.

Based on the 95% upper confidence bound for the difference in proportions for mean and by-visit scores, the test might exceed the reference by at most 18.2 and 23.9 percentage points with regard to the proportion of subjects who had mean and visit at hour 48 adhesion scores greater than 0.

Moreover, considering the difference in proportions for mean and by-visit scores, the test might exceed the reference by at most 1.7 and 2.1 percentage points with regard to the proportion of subjects who had mean and visit at hour 12 adhesion scores greater than 3, i.e., full detachment.

4 SUMMMARY AND CONCLUSIONS

4.1 Statistical Issues and Findings

Primary endpoint: The mean cumulative adhesion score was analyzed using a mixed linear model. Non-inferiority analyses based on the mean cumulative adhesion scores showed that the one-sided 95% upper CB for the adjusted mean difference (μ_T -1.25μ_R) was larger than zero (0.068) and the non-inferiority test was failed for test versus reference patch. Therefore, the adhesion potential of the test is worse than that of the reference.

Based on the 95% upper confidence bound for the difference in proportions for mean and by-visit scores, (1) the test might exceed the reference by at most 18.2 and 23.9 percentage points with regard to the proportion of subjects who had mean and visit at hour 48 adhesion scores greater than 0; (2) the test might exceed the reference by at most 1.7 and 2.1 percentage points with regard to the proportion of subjects who had mean and 12 hour visit adhesion scores greater than 3 (full detachment).

Main difference between sponsor's results and our results:

Where the sponsor's results differ from our results, mainly it is due to the following reasons.

a) Sponsor analyzed the sum cumulative adhesion score. We used the mean cumulative adhesion score.
b) Sponsor carried out a non-parametric analysis to compare the median of test versus reference using bootstrap approach. We did not repeat their analysis.
c) Sponsor carried out a binary analysis for the proportion of patches that completely detached and concluded the test patch is non-inferior to the reference patch. In our secondary endpoint analysis for the difference in proportion for mean and by-visit scores, the test might exceed the reference by at most 1.7 and 2.1 percentage points with regard to the proportion of subjects who had mean and visit at hour 12 adhesion scores greater than 3 (full detachment). In OGD clinical review, the secondary endpoint results are used only as supplementary information.

4.2 Conclusions

The primary analysis of mean scores showed that the test patch was found to be worse than the reference patch for adhesion based on the results from the mixed linear model.

Secondary endpoints: Based on the 95% upper confidence bound for the difference in proportions for adhesion scores, (1) the test might exceed the reference by at most 18.2 and 23.9 percentage points with regard to the proportion of subjects who had mean and 48 hour visit adhesion scores greater than 0; (2) the test might exceed the reference by at most 1.7 and 2.1 percentage points with regard to the proportion of subjects who had mean and 12 hour visit adhesion scores greater than 3 (full detachment).

_____	_____
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ANDA/Serial Number:	078830 (Study No. 11325301)
Drug Name:	Scopolamine Transdermal System, 1.31 mg
Indication(s):	Motion sickness and recovery from anesthesia and surgery
Reference Listed Drug:	Transderm Scop® (Novartis) 1.5mg
Applicant:	Perrigo R & D Company.
Date(s):	Submitted March 14, 2014
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Keywords:	adhesion, non-inferiority, mixed model, matched pair analysis

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1 EXECUTIVE SUMMARY

1.1 Conclusions and recommendations

The primary analysis of mean scores showed that the test patch was found to be worse than the reference patch for adhesion based on the results from the mixed linear model.

1.2 Brief overview of clinical studies

This review is for an additional adhesion study (No. 11325301) submitted to FDA dated March 14, 2014.

ANDA 078830 was submitted to FDA on February 23, 2007 which included two studies: a two-period irritation and sensitization study of the test system, using the test placebo patch (Protocol PRG-603); and a pharmacokinetic study that additionally evaluated adhesion of the test system, using the active test patch (Protocol PRG-604).

FDA sent out a deficiencies letter on May 31, 2013 which contained the comments: "***In the pharmacokinetic/adhesion study (PRG-604), your product was statistically significantly less adhesive than the reference product. The study failed to show noninferiority of your Scopolamine Extended-release Transdermal Film to the reference product with regard to adhesion performance.***"

Perrigo acknowledged Agency's comment and conducted a standalone adhesion study (No. 11325301) in order to generate adequate data to ensure that the adhesive performance of Perrigo's Scopolamine Transdermal Delivery System 1.31mg is at least as good as reference product Transderm Scop® 1.5mg.

Study 11325301 was a multiple-center, single-application, randomized, two-treatment, two-period, four-sequence, crossover study comparing the adhesive properties of the test patch, scopolamine transdermal therapeutic system, 1.31 mg (manufactured by AVĒVA Drug Delivery Systems, an Apotex Company; distributed by Perrigo), relative to those of the reference patch, TRANSDERM-SCŌP® (scopolamine) transdermal therapeutic system, 1.5 mg (manufactured by ALZA Corporation; distributed by Novartis Consumer Health, Inc.).

1.3 Statistical issues and findings

I) The mean cumulative adhesion scores were analyzed using a mixed linear model. The one-sided 95% upper CB for the adjusted mean difference ($\mu_T - 1.25\mu_R$) was greater than zero (0.068) and the non-inferiority test was failed for test versus reference. Hence, the adhesion property of the test product is considered worse than that of the reference product.

II) Based on the 95% upper confidence bound for the difference in proportions for mean and by-visit scores, the test might exceed the reference by at most 18.2 and 23.9 percentage points with

regard to the proportion of subjects who had mean and visit at hour 48 adhesion scores greater than 0.

2 INTRODUCTION

2.1 Overview

The Transderm Scop® (scopolamine extended-release transdermal film) system is a circular flat patch containing 1.5 mg of scopolamine base and designed to deliver approximately 1.0 mg of scopolamine over 3 days. It is indicated in adults for prevention of nausea and vomiting associated with motion sickness and recovery from anesthesia and surgery. The patch is to be applied only to skin in the post auricular area. Only one patch should be worn at any time, and the patch, which has a reservoir design, is not to be cut. One patch is to be applied for up to 72 hours and it can be replaced if necessary.

The data were submitted electronically. The data files are located in the following directory:

\\cdsesub1\evsprod\anda078830**0012**\m5\datasets**11325301**\listings

In this report, all tables, unless otherwise specified, are taken from FDA clinical reviewer's or the sponsor's report. Analysis results and tables calculated by FDA statistical reviewer are noted as such in the text and/or the title of the tables.

3 STATISTICAL EVALUATION

3.1 Statistical methodologies

The statistical methods used in analysis are described in this section.

In the study, each subject received two patches: test patch in one period and reference patch in another period with sequence randomized. As a result, observations taken from the same subject might be correlated. For the analysis of continuous data, linear mixed models were used in the comparison of means; the random effects in the mixed model structure assessed and reflected the correlation of observations. For matched dichotomized pairs data, the McNemar test was used to compare the test and the comparator in the difference between 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 adhesion score.

The statistical method for continuous data uses the estimate of the adjusted mean difference $\mu_T - 1.25\mu_C$, to test the hypotheses

H_0: $\mu_T - 1.25\mu_C > 0$ vs H_1: $\mu_T - 1.25\mu_C \leq 0$

where μ_T is the mean response for the test and μ_C is the mean response for the comparator. One-sided 95% confidence intervals (CIs) were obtained based on the estimated means. If the upper limit of the CI is less than or equal to 0, the null hypothesis is rejected and the test patch may be considered non-inferior to the comparator. Otherwise it is concluded that the test may be worse than the comparator. The comparator is the reference patch in this study.

The SAS® (Version 9.2) 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*Comparator' 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 the mean adhesion score, and adhesion score per evaluation hour. Method based on the work of McNemar was used to compare the test and comparator with regard to the binary endpoints (proportions).

For the method used to assess the non-inferiority of the test versus comparator, a 95% upper confidence bound for the difference of the proportions between test and comparator was calculated.

Let
p_T = rate of the test, p_C = rate of the comparator (p_T and p_C were adhesion rates in this analysis);
n = total number of subjects;
b = number of subjects with a negative outcome (detachment) using the test but not the comparator;
and c = number of subjects with a negative outcome (detachment) using the comparator but not the test.
Hypotheses: H_0: $p_T - p_C > \delta$ vs H_1: $p_T - p_C \leq \delta$

Data on two outcomes from matched pairs

		Test	
		Score<=crit	Score> crit
Comparator	Score<=crit	a	b
	Score> crit	c	d

Total n=a+b+c+d

*: Critical value (crit) was used to dichotomize the score.

The difference of p_T - p_C may be estimated by the quantity (b – c)/n.

Based on McNemar's test, the 95% upper confidence bound (U) for the quantity p_T - p_C was calculated as

$$U = \frac{(b-c)}{n} + \frac{1}{n} + 1.645 \frac{\sqrt{(b+c) - \frac{(b-c)^2}{n}}}{n}$$

This formula for the upper confidence bound is algebraically the same as that given by Fleiss (1981, p117).

For any given non-inferiority bound δ, the null hypothesis H_0 may be rejected if this 95% upper confidence bound U for the quantity p_T - p_C is less than or equal to δ, that is: $U \leq \delta$. Rejection of the null hypothesis H_0 supports the conclusion of non-inferiority of the test to the comparator. The non-inferiority standard δ is yet to be decided by OGD.

3.2 Study No. 11325301: Evaluation of adhesion

3.2.1 Study design and endpoints

Study Objective

The primary objective was to compare the adhesive properties of a test scopolamine transdermal therapeutic system, 1.31 mg (Perrigo) relative to those of the marketed reference formulation, TRANSDERM-SCŌP® in healthy adult subjects.

Study design

This was a multiple-center, single-application, randomized, two-treatment, two-period, four-sequence, crossover study comparing the adhesive properties of the test and reference patch.

Subjects had one (1) scopolamine transdermal therapeutic system applied behind the ear (postauricular area) and kept in place for approximately 72 hours in each period of the study. Subjects received the test product in one of the study periods and the reference product in the other study period according to the randomization schedule. As the primary objective of this study was to compare adhesion, there was no washout period between the study periods.

Immediately after application (0 hour) and at 12, 24, 36, 48, 60, and 72 hours (before patch removal) after application (±60 minutes) the patches were checked for the degree of adhesion by a trained scorer using the FDA-recommended rating scale.

The study was conducted with 80 (71 completing, 77 included in PPPA) healthy adult subjects in accordance with Protocol No. PRG-NY-14-007 (Revision 1).

Treatments

Treatment	Description
Product A (Test)	Scopolamine transdermal therapeutic system, 1.31 mg (manufactured by AVĒVA Drug Delivery Systems, an Apotex Company; distributed by Perrigo),
Product B (Reference)	TRANSDERM-SCŌP® (scopolamine) Transdermal therapeutic system, 1.5 mg (manufactured by ALZA Corporation; distributed by Novartis Consumer Health, Inc.)

Adhesion evaluations

0 =	≥90% 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=	>0% to <50% adhered, but not detached (more than half the system lifting off of the skin without falling off)
4 =	0% adhered - patch detached (patch completely off the skin)

Clinical endpoints

Primary endpoint: Mean Cumulative Adhesion Scores

The mean cumulative adhesion scores were obtained by adding total observations at 12, 24, 36, 48, 60, and 72 hours in the application period and dividing by the number of observations (6).

Secondary endpoints: The clinical reviewer requested a comparator of test versus reference with regard to the proportion of patch applications with meaningful detachment. The analyses were conducted to compare the test and reference with regard to the proportion of subjects who had mean and visit adhesion scores greater than 0, 1, 2, and 3.

3.2.2 Subject disposition

A total of 80 healthy adult subjects were enrolled and 77 subjects were included in the sponsor's Per Protocol (ADHPP) and FDA's Per Protocol (ADHFPP) populations for adhesion analysis.

Three subjects were excluded from the ADHPP/ADHFPP populations.

- Subject (b) (6) did not return as scheduled for the Period I 60 hour adhesion assessment and thus was considered to have voluntarily withdrawn from the study.
- Subject (b) (6) was discontinued by the Investigator following removal of the Period I patch on Day 4 for a protocol deviation for the subject's use of dextroamphetamine sulfate for recreational purposes on Day 3.

- Subject (b) (6) voluntarily withdrew from the study for personal reasons before the Period I 72 hour adhesion assessment.

Eight subjects, (b) (6), experienced complete detachment of the patch application in the ADHPP/ADHFPP population. Data from these subjects were included in the analyses with a score of 4 (complete patch detachment) carried forward (LOCF) shown below.

		Adhesion score					
Subject	Treatment	12 Hours	24 hours	36 Hours	48 Hours	60 Hours	72 Hours
(b) (6)	Reference	0	0	0	4	4	4
	Reference	0	0	0	0	4	4
	Reference	0	0	4	4	4	4
	Reference	0	0	4	4	4	4
	Test	0	0	1	4	4	4
	Reference	0	0	0	0	4	4
	Reference	0	4	4	4	4	4
	Reference	4	4	4	4	4	4

The demographic characteristics of the ADHFPP population were summarized in Table 1.

Table 1: Demographic characteristics (ADHFPP, N=77)

Age (years)	
Mean (Range)	41.38 (20-64)
Gender	
Female	39 (50.65%)
Male	38 (49.35%)
Race	
White	23 (29.87%)
Black/African American	36 (46.75%)
Others	18 (23.38%)

3.2.3 Results and conclusions

3.2.3.1 Sponsor's analysis results

The sponsor concluded the test patch is non-inferiority to the reference patch based on their analysis below.

"The primary endpoint of adhesion was the Cumulative Adhesion Score (CAS) during the 72-hour application period.

The primary objective related to adhesion was whether the level of adhesion of the test patch is no worse than (non-inferior to) that of the reference patch. Because the adhesion scale shows better adhesion for lower values, the relevant hypotheses for evaluating non-inferiority are:
H0: T - (1.25 x R) > 0 (not non-inferior)

H1: T - (1.25 x R) ≤ 0 (non-inferior)

As the CAS were shown not to be normally distributed, a non-parametric method was used for treatment comparison.
For non-parametric analysis, the appropriate hypotheses are:
H0: Median (T - 1.25R) > 0 (not non-inferior)
H1: Median (T - 1.25R) ≤ 0 (non-inferior)
The Bootstrap approach was used to test the significance in hypothesis testing.

The upper bound for the 95% one-sided confidence interval was equal to zero (0). Therefore, the adhesion of the test patch was considered to be non-inferior to that of the reference patch.

The number and proportion of patches that completely detached are presented in Table 2.3.

Table 2.3 Proportion of Patches that Completely Detached (PPPA)

		Adhesion Score	
Product*	**N**	**≤ 3 (not detached) N (%)**	**4 (detached) N (%)**
A	77	76 (98.70)	1 (1.30)
B	77	70 (90.91)	7 (9.09)

*A = Scopolamine Transdermal Delivery System, 2.5 cm^2, label claim 1.31 mg/unit (Manufactured by AVĒVA Drug Delivery Systems, an Apotex Company; Distributed by Perrigo)
B = TRANSDERM-SCŌP® (scopolamine) transdermal system, 1.5 mg (Manufactured by ALZA Corporation; Distributed by Novartis Consumer Health, Inc.)

CONCLUSION: *The adhesion of the test scopolamine transdermal therapeutic system, 1.31 mg (manufactured by AVĒVA Drug Delivery Systems, an Apotex Company; distributed by Perrigo) was shown to be statistically non-inferior to that of the reference product, TRANSDERM-SCŌP® (scopolamine) transdermal therapeutic system, 1.5 mg (manufactured by ALZA Corporation; distributed by Novartis Consumer Health, Inc.), in the primary non-parametric analysis."*

3.2.3.2 Reviewer's results

The analysis is based on FDA's Per Protocol population (same as the sponsor's PP population) and follows the guidance-recommended approach.

Table 2: Frequency of adhesion scores (N=77)

Evaluation hours	Treatment	Adhesion score				
		0	1	2	3	4
12	Test	73	4			
	Reference	76				1
24	Test	68	9			
	Reference	71	4			2
36	Test	59	17	1		
	Reference	68	5			4
48	Test	55	17	4		1
	Reference	64	7	1		5
60	Test	54	18	3	1	1
	Reference	59	9	2		7
72	Test	52	18	4	2	1
	Reference	57	11	2		7

Primary endpoint: Mean cumulative adhesion score

The frequency of mean cumulative adhesion scores per each patch is shown in Table 3. The mean cumulative adhesion scores were analyzed using a mixed model and are presented in Table 4.

Table 3: Frequency of mean cumulative adhesion scores (N=77)

	0	0.17	0.33	0.5	0.67	0.83	1	1.17	1.33	1.67	1.83	2	2.17	2.67	3.33	4
Test	52	2	1	3	6	6	2	1	1	1	1		1			
Reference	56	2	2	3	4	3			2			1		2	1	1

Table 4: Analysis for the mean cumulative adhesion scores using mixed model (N=77)

	Test (Ls mean)	Reference (Ls mean)	Upper limit one-sided 95%CB (test-1.25ref)	Pass the Non-inferiority test
Mean	0.2771	0.3247	0.068	No

Non-inferiority analyses based on the mean cumulative adhesion scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference (μ_T -1.25μ_R) was larger than zero (0.068) and the non-inferiority test was failed for test versus reference patch. Therefore, the adhesion potential of the test is worse than that of the reference.

Secondary endpoint: Dichotomized adhesion scores

Table 5: Analysis of the dichotomized adhesion score for score>crit versus others (N=77)*

Crit	0			1			2			3		
	b	c	UB	b	c	UB	b	c	UB	b	c	UB
Mean	17	13	0.182	4	6	0.054	1	4	0.021	0	2	0.017
Visit (Hour)												
12	4	1	0.099	0	1	0.021	0	1	0.021	0	1	0.021
24	8	5	0.129	0	2	0.017	0	2	0.017	0	2	0.017
36	16	7	0.230	1	4	0.021	0	4	0.003	0	4	0.003
48	18	9	0.239	3	4	0.056	1	5	0.012	1	5	0.012
60	17	12	0.192	4	8	0.034	2	7	0.011	1	7	-0.006
72	17	12	0.192	6	8	0.067	3	7	0.028	1	7	-0.006

*: Critical value (crit) was used to dichotomize the score.
b = number of subjects with a negative outcome (detachment, score>crit) using the test but not the reference;
c = number of subjects with a negative outcome (detachment, score>crit) using the reference but not the test.
UB (95% Upper Bound) for $P_T - P_R$ = P (mean cumulative/visit adhesion score greater than crit for test) - P (mean cumulative/visit adhesion score greater than crit for reference).

In addition to the primary endpoint analyses, analyses for the secondary endpoints were conducted to compare the test and reference with regard to the proportion of subjects who had mean and visit adhesion scores greater than 0, 1, 2, and 3.

Based on the 95% upper confidence bound for the difference in proportions for mean and by-visit scores, the test might exceed the reference by at most 18.2 and 23.9 percentage points with regard to the proportion of subjects who had mean and visit at hour 48 adhesion scores greater than 0.

4 SUMMMARY AND CONCLUSIONS

4.1 Statistical Issues and Findings

Primary endpoint: The mean cumulative adhesion score was analyzed using a mixed linear model. Non-inferiority analyses based on the mean cumulative adhesion scores showed that the one-sided 95% upper CB for the adjusted mean difference (μ_T -1.25μ_R) was larger than zero (0.068) and the non-inferiority test was failed for test versus reference patch. Therefore, the adhesion potential of the test is worse than that of the reference.

Based on the 95% upper confidence bound for the difference in proportions for mean and by-visit scores, the test might exceed the reference by at most 18.2 and 23.9 percentage points with regard to the proportion of subjects who had mean and visit at hour 48 adhesion scores greater than 0.

Main difference between sponsor's results and our results:

Where the sponsor's results differ from our results, mainly it is due to the following reasons.

a) The sponsor analyzed the sum cumulative adhesion score. We used the mean cumulative adhesion score.
b) The sponsor carried the non-parametric analysis to compare the median of test versus reference using bootstrap approach. We did not repeat their analysis.

4.2 Conclusions

The primary analysis of mean scores showed that the test patch was found to be worse than the reference patch for adhesion based on the results from the mixed linear model.

Secondary endpoints: Based on the 95% upper confidence bound for the difference in proportions for adhesion scores, the test might exceed the reference by at most 18.2 and 23.9 percentage points with regard to the proportion of subjects who had mean and 48 hour visit adhesion scores greater than 0.

_____	_____
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ANDA/Serial Number:	078830
Drug Name:	Scopolamine Extended-release Transdermal Film, 1 mg/72 hr
Indication(s):	Motion sickness and recovery from anesthesia and surgery
Reference Listed Drug:	Transderm Scop® (Novartis)
Applicant:	Perrigo R & D Company.
Date(s):	Submitted February 23, 2007
Biometrics Division:	DB6
Statistical Reviewer:	Huaixiang Li, Ph.D.
Concurring Reviewers:	Stella Grosser, Ph.D.
Medical Division:	Division of Clinical Review (DCR) in OGD
Clinical Team:	Sarah H. Seung, Pharm.D.
Keywords:	irritation, sensitization, adhesion, non-inferiority, matched pair analysis

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1 EXECUTIVE SUMMARY

1.1 Conclusions and recommendations

The primary analysis of mean scores showed that the test placebo patch[1] was found to be non-inferior to the mild irritant patch (control) for irritation and the test patch was found to be worse than the reference patch for adhesion, based on the results from the mixed linear model.

No subject was considered to be potentially sensitized for the test placebo patch,

1.2 Brief overview of clinical studies

This application included two studies: a two-period irritation and sensitization study of the test system, using the test placebo patch (Protocol PRG-603); and a pharmacokinetic study that additionally evaluated adhesion of the test system, using the active test patch (Protocol PRG-604).

Study **PRG-603** was a 6-week, multiple study-site, multiple-application, challenge study in two hundred ninety six (296) healthy subjects. The study consisted of two phases, an irritation/induction phase (Study Day 1 to Day 22) and a challenge phase (Study Day 36 to Day 41) to evaluate sensitization. A fourteen day rest period, during which no patches were applied, separated the two phases of the study.

Subjects received both a test placebo patch and mild irritant patch, with side of the neck randomized, in the irritation phase. In the challenge phase, only the test placebo patch was used, an option given in the FDA Guidance due to the need for a naïve site to apply the patch.

Study **PRG-604** was primarily designed as a single site, open-label, randomized, two-way crossover pharmacokinetic study conducted on 30 healthy adult subjects under fasting conditions. As an additional feature, adhesion scores were obtained and compared for both patches in this study. This review considers only the adhesion outcomes of the study; the PK parameters are analyzed elsewhere.

Subjects in study PRG-604 received test patch in one period and reference patch in another period. Each period lasted 5 days, with single 1.0 mg scopolamine patch administrations separated by a washout period of 7 days. Because the primary purpose of this study was to assess blood concentrations, in each period, subjects were housed in the clinic from approximately 12 hours before dosing until after the 120-hour post-dose events.

1.3 Statistical issues and findings

Irritation study

[1] Test placebo patch has all of the same inactive ingredients and is identical to the sponsor's proposed product in every manner except for the absence of the active ingredient itself.

I) The non-inferiority analyses based on the mean cumulative irritation scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference (μ_{TP} - $1.25\mu_{MI}$) was less than zero. Thus the non-inferiority test was passed for test placebo patch versus mild irritant patch and the irritation potential of the test placebo patch is considered not worse than that of the mild irritant patch.

II) Analyses based on dichotomized mean cumulative irritation scores:
Based on the 95% upper confidence bound for the difference in proportions, the test placebo might exceed the mild irritant by at most -2.96 (negative) percentage points with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 1. And also the test placebo might exceed the mild irritant by at most 0.75 percentage points with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 2.

Sensitization study

No subject was considered to be potentially sensitized for the test placebo patch.

Adhesion study

I) The mean cumulative adhesion scores were analyzed using a mixed linear model. The one-sided 95% upper CB for the adjusted mean difference (μ_T -$1.25\mu_R$) was greater than zero (0.1059) and the non-inferiority test was failed for test versus reference. Hence, the adhesion property of the test product is considered worse than that of the reference product.

II) Based on the 95% upper confidence bound for the difference in detachment rates, the test might exceed the reference by at most 14.8% for the proportion of subjects who had mean adhesion score greater than or equal to 1 (≥ 10 detached) and 18.9% for the proportion of subjects who had mean adhesion score greater than or equal to 2 ((≥ 25 detached).

2 INTRODUCTION

2.1 Overview

The Transderm Scop® (scopolamine extended-release transdermal film) system is a circular flat patch containing 1.5 mg of scopolamine base and designed to deliver approximately 1.0 mg of scopolamine over 3 days. It is indicated in adults for prevention of nausea and vomiting associated with motion sickness and recovery from anesthesia and surgery. The patch is to be applied only to skin in the post auricular area. Only one patch should be worn at any time, and the patch, which has a reservoir design, is not to be cut. One patch is to be applied for up to 72 hours and it can be replaced if necessary.

This application for a generic scopolamine system includes two clinical studies: a two-period irritation and sensitization study of the test system, using a test placebo patch (Protocol PRG-603); and a pharmacokinetic study that additionally evaluated adhesion of the test system, using

the active test patch (Protocol PRG-604). These studies are summarized here and described in greater detail in Sections 3.2 and 3.3.

Study **PRG-603** was a 6-week, multiple site, multiple-application, challenge study in two hundred ninety six (296) healthy subjects. The study consisted of two phases, an irritation/induction phase (Study Day 1 to Day 22) and a challenge phase (Study Day 36 to Day 41) to evaluate sensitization. A fourteen day rest period, during which no patches were applied, separated the two phases of the study.

Subjects received both a test placebo patch and mild irritant patch, with side of the neck randomized, in the irritation phase. In the challenge phase, only the test placebo patch was used, an option given in the FDA Guidance due to the need for a naïve site to apply the patch.

Study **PRG-604** was primarily designed as a single site, open-label, randomized, two-way crossover pharmacokinetic study conducted on 30 healthy adult subjects under fasting conditions. As an additional feature, adhesion scores were obtained and compared for both patches in this study. This review considers only the adhesion outcomes of the study; the PK parameters are analyzed elsewhere.

Subjects in study PRG-604 received test patch in one period and reference patch in another period. Each period lasted 5 days, with single 1.0 mg scopolamine patch administrations separated by a washout period of 7 days because the primary purpose of this study was to assess blood concentrations, in each period, subjects were housed in the clinic from approximately 12 hours before dosing until after the 120-hour post-dose events.

2.2 Data sources

The data were submitted electronically. The data files are located in the following directories:

Protocol PRG-603: Irritation and Sensitization study
\\cdsesub1\EVSPROD\ANDA078830**0000**\m5\datasets\study-report-prg-**603**\listings

Protocol PRG-604: Adhesion study
\\cdsesub1\EVSPROD\ANDA078830**0000**\m5\datasets\study-report-prg-**604**\listings

In this report, all tables, unless otherwise specified, are taken from FDA clinical reviewer's or the sponsor's report. Analysis results and tables calculated by FDA statistical reviewer are noted as such in the text and/or the title of the tables.

3 STATISTICAL EVALUATION

3.1 Statistical methodologies

The common statistical methods used in analysis across the two studies are described in this section. As the endpoints are different in the two studies, they are defined in the study-specific sections 3.2 and 3.3.

In both studies, each subject received two patches: test placebo and mild irritant patches simultaneously in the skin irritation study, with side of neck on which the patch was placed assigned randomly; test patch in one period and reference patch in another period in the adhesion study, with sequence randomized. As a result, observations taken from the same subject might be correlated. For the analysis of continuous data, linear mixed models were used in the comparison of means; the random effects in the mixed model structure assessed and reflected the correlation of observations. For matched dichotomized pairs data, the McNemar, Clopper-Pearson, and, Schuirmann tests were used to compare the test and the comparator in the difference between 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 or adhesion score (depending on study).

The statistical method for continuous data uses the estimate of the adjusted mean difference $\mu_T - 1.25\mu_C$, to test the hypotheses

$H_0: \mu_T - 1.25\mu_C > 0$ vs $H_1: \mu_T - 1.25\mu_C \leq 0$

where μ_T is the mean response for the test and μ_C is the mean response for the comparator. One-sided 95% confidence intervals (CIs) were obtained based on the estimated means. If the upper limit of the CI is less than or equal to 0, the null hypothesis is rejected and the test patch may be considered non-inferior to the comparator. Otherwise it is concluded that the test may be worse than the comparator.

The SAS® (Version 9.2) 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*Comparator' 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 day, dichotomized mean adhesion score, and adhesion score per evaluation hour. Methods based on the work of McNemar, Clopper-Pearson, and Schuirmann were used to compare the test and comparator with regard to the binary endpoints (proportions).

The McNemar test is a common method for matched pair dichotomized analysis. The Clopper-Pearson method is considered as an "exact" test specifically 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 comparator, a 95% upper confidence bound for the difference of the proportions between test and comparator was calculated.

Let
p_T = rate of the test, p_C = rate of the comparator (p_T and p_C might be irritation rates, or adhesion rates, depending on the analysis);
n = total number of subjects;
b = number of subjects with a negative outcome (irritation or detachment) using the test but not the comparator;
and c = number of subjects with a negative outcome (irritation or detachment) using the comparator but not the test.
Hypotheses: H_0: $p_T - p_C > \delta$ vs H_1: $p_T - p_C \leq \delta$

Data on two outcomes from matched pairs

		Comparator	
		Score>=crit	Score<crit
Test	Score>=crit	a	b
	Score<crit	c	d
Total n=a+b+c+d			

*: Critical value (crit) was used to dichotomize the score.

The difference of $p_T - p_C$ may be estimated by the quantity (b – c)/n.

Based on McNemar's test, the 95% upper confidence bound (U) for the quantity $p_T - p_C$ was calculated as

$$U = \frac{(b-c)}{n} + \frac{1}{n} + 1.645\frac{\sqrt{(b+c) - \frac{(b-c)^2}{n}}}{n}$$

This formula for the upper confidence bound is algebraically the same as that given by Fleiss (1981, p117).

Based on Clopper-Pearson test (1934), the 95% upper confidence bound (U) for the quantity $p_T - p_C$ was calculated as:

$$U = \left[1+\frac{n-x}{(x+1)F_{2(x+1),2(n-x),\alpha/2}}\right]^{-1} \qquad \text{if } b \geq c$$

or,

$$U = -\left[1+\frac{n-x+1}{xF_{2x,2(n-x+1),1-\alpha/2}}\right]^{-1} \qquad \text{if } b < c$$

where x = | b-c | and α=0.10. $F_{2(x+1),\,2(n-x),\,\alpha/2}$ denotes the (1-α/2) quantile from the F distribution with degree of freedom 2(x+1) and 2(n-x). $F_{2x,\,2(n-x+1),\,1-\alpha/2}$ denotes the α/2 quantile from the F distribution with degree of freedom 2x and 2(n-x+1).

Based on the Schuirmann (2008) test, the 95% upper confidence bound (U) for the quantity p_T - p_C was calculated as follows.

Let $$Z = \frac{\hat{\delta}+CC-U}{\sqrt{\frac{\xi^{*}-U^{2}}{n}}},$$

Here, $\hat{\delta}=\frac{b-c}{n}, CC=\frac{1}{n}, \xi^{*}=\max(\frac{b+c}{n},|U|)$.

The value of U is the 95% upper confidence bound for the quantity p_T - p_C when Z is equal to $Z_{\alpha/2}$ = -1.645, α=0.10.

For any given non-inferiority bound δ, the null hypothesis H_0 may be rejected if this 95% upper confidence bound U for the quantity p_T - p_C is less than or equal to δ, that is: U ≤ δ. Rejection of the null hypothesis H_0 supports the conclusion of non-inferiority of the test to the comparator. The non-inferiority standard δ is yet to be decided by OGD.

3.2 Protocol PRG-603: Evaluation of irritation and sensitization

3.2.1 Study design and endpoints

Objectives

The objective of this study was to evaluate the skin irritation potential for Test placebo patch compared to Mild irritant patch and sensitization potential for Test placebo patch when applied over a continuous 21 day period for both patches in the irritation phase followed by a single dose of Test placebo patch in the challenge phase.

Study design

This study was a 6-week, multiple site, multiple-application, challenge study in healthy subjects. The study consisted of two phases, an irritation/induction phase (Study Day 1 to Study Day 22) and a challenge phase (Study Day 36 to Day 41) to evaluate sensitization. A fourteen day rest period, during which no patches were applied, separated the two phases of the study.

During the first period of the applications (induction/irritation Phase, Day 1 through 22) the patches were repeatedly applied to the same sites behind the subject's ear following the randomization schedule. During the irritation/induction phase, patches were applied and replaced on Days 1, 4, 7, 10, 13, 16, and 19.

After each patch was removed (each patch was applied for three days) a window of ± 2 hours was allowed for all assessments. After the last removal, on Day 22, all subjects underwent a 14 day rest phase when no patches were applied.

For the challenge application (Day 36), the same randomization was used. For example, if the subject received the test placebo patch behind the left ear in the induction/irritation Phase, it was placed on the left lower neck in the challenge phase. As allowed by the Guidance, only the test placebo patch was applied on Day 36[2]. It was removed on Day 38, after 48 hrs (± 2 hours) of application. The sites were scored approximately 0.5, 24, 48, and 72 hours (±1 hour) after patch removal using the sensitization scoring scale.

Irritation study: Induction period (Study Days 1 to 22)	Rest period (Study Days 23 to 35)	Sensitization study: Challenge period (Study Days 36 to 41)

Treatments

Article	Description
Test*	Placebo Scopolamine Transdermal Delivery System; Aveva Drug Delivery Systems, Inc. Lot No. 35411 Date of Manufacture: 06/19/2006
Mild irritant**	0.05 ml of 0.1% sodium lauryl sulfate solution applied to Band-Aid® Perfect Blend™ clear bandages, 2.2 cm x 2.2 cm; Novum Pharmaceutical Research Services

* The test placebo patches were manufactured at a facility owned by Aveva Drug Delivery Systems, Inc.
** The mild irritant patches were prepared at each clinical site by designated personnel.

Outcome variables

The following scales were used by the sponsor for evaluating irritation and sensitization:

Scoring Scale for Evaluation of Induction and Challenge Phase Applications:

[2] Detailed explanation is in the clinical review report.

Irritation Scoring

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

0	No other observations
1	Slight glazed appearance
2	Marked glazed appearance
3	Glazing with peeling and cracking
4	Glazing with fissure
5	Film of dried serous exudates covering all or part of the patch site
6	Small petechial erosions and/or scabs

FDA clinical reviewer pointed: "*This change in the scale [by the sponsor from the FDA's recommended scoring] may impact the study results. Therefore, the FDA statistician is requested to analyze the sponsor's data using the FDA generally accepted scoring system.*"

Other Effects Scoring System: FDA and Sponsor Scale

Sponsor Score	FDA Letter Score	FDA Numeric Score	Description
1	A	0	Slight glazed appearance/peeling of skin observed
2	B	1	Marked glazed appearance/peeling of skin observed
3	C	2	Definite peeling and cracking observed
4	F	3	Fissures observed
5	G	3	Film of dried serous exudates covering all or part of the patch site
6	H	3	Small petechial erosions and/or scabs

Endpoints

Irritation study

Primary endpoint:

Mean cumulative irritation scores per subject for each test article were obtained by averaging all irritation scores over the induction period (Study Day 4, 7, 10, 13, 16, 19, and 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 ≥ 1 on Day 4, 7, 10, 13, 16, 19, and 22
- Proportion of subjects who had irritation scores ≥ 2 on Day 4, 7, 10, 13, 16, 19, and 22.

Sensitization study

Primary endpoint:

To identify subjects showing a potential sensitizing reaction, we used the following definition based on the FDA Draft Guidance on Scopolamine Film, Extended Release/Transdermal, 1 mg/72 hr (October, 2011).

"…. a subject [is considered] to be potentially sensitized if all of the following criteria are met:

a. 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.

b. The subject has a combined "Dermal Response" and "Other Effects" numeric score of at least 2 at their last evaluation during the Challenge Phase.

c. 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.

d. 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."

3.2.2 Subject disposition

Two hundred ninety-six (296) patients were enrolled and randomized. The sponsor's Irritation Per Protocol population (IRRPPP) and Sensitization Per Protocol population (SNSPPP) had some difference from the FDA's Irritation Per Protocol population (IRRFPP) and Sensitization Per Protocol population (SNSFPP). The patient disposition for the sponsor's and FDA's populations is given in Table 1.

Table 1: Patient disposition

	Test placebo	Mild irritant
Enrolled and Randomized	**296**	**296**
Sponsor's IRR PP population (IRRPPP)	**239**	**241**
Total exclusion from the sponsor's IRRPPP population	57	55
Reason for exclusion from sponsor's IRRPPP		
Adverse event	8	5
Non-compliant	24	24
Voluntary withdrawal	25	25
No reason in the dataset[#]		1
Sponsor's SNS PP population (SNSPPP)	**228**	
Total exclusion from the sponsor's SNSPPP population	68	
Reason for exclusion from sponsor's SNSPPP		
Adverse event	10	
Non-compliant	29	
Voluntary withdrawal	27	
Other	2	
FDA's IRR PP population (IRRFPP)	**240**	**228**
Total exclusion/inclusion from the FDA's IRRFPP population	56	68
Exclusion from sponsor's IRRPPP	57	55
Didn't have patch applied on Day 10[*1]		12
Patch free for > 24 hours[*2]	1	2
FDA clinical reviewer recommend[*3]	+2	+1
FDA's SNS PP population (SNSFPP)	**220**	
Total exclusion from the FDA's SNSFPP population	76	
Exclusion from sponsor's SNSPPP	68	
Subject had <45 hours of patch wear in challenge phase[@1]	7	
Records description[@2]	1	

Note; Patient may have multiple reasons to be excluded from the populations.
#: There was no explanation given in the electronic summary dataset for the exclusion of Subject (b) (6) (mild irritant) from the IRRPPP population. According to FDA clinical reviewer's comment, this subject didn't apply mild irritant patch at Day 10.
FDA clinical reviewer's comment:
*1: The 16 subjects who did not have the mild irritant patch (TRT B) applied on Day 10 and were patch free for >24 hours should be excluded from the TRT B Irritation PP population: (b) (6) (b) (6) Subject (b) (6) were already excluded from the IRRPPP.
*2: Subject (b) (6) (TRT B), (b) (6) (TRT B), and (b) (6) (TRT A) were patch free for >24 hours.
*3: Subject (b) (6) (TRT B), (b) (6) (TRT A), and (b) (6) (TRT A) were included in the IRRFPP.
@1: Subject (b) (6) had <45 hours of patch wear for the challenge patch due to the challenge patch detaching completely.
@2: Subject (b) (6) is noted to have the challenge patch applied on 10/13/06 at 8:38am and the patch removed on the same date (10/13/06) at 9:01am. However, the 30-min skin assessment did not occur until 10/15/06.

Remark: There was a total of 246 subjects in the IRRFPP. There were 222 subjects who had both patches (Test and Mild irritant), 18 subjects who had only Test patch, and 6 subjects who had only Mild irritant patch.

Demographics

Table 2 shows the distribution of age, gender, and race for the IRRFPP and SNSFPP population.

Table 2: Demographic characteristics (IRRFPP and SNSFPP)

	IRRFPP (N=246)	SNSFPP (N=220)
Age (years)		
Mean (Range)	39.47 (18-71)	39.77 (18-71)
Gender		
Female Male	166 (67.48%) 80 (32.52%)	145 (65.91%) 75 (34.09%)
Race		
White Black/African American Hispanic or Latino Native Hawaiian or other pacific island Other	76 (30.89%) 144 (58.54%) 18 (7.32%) 1 (0.41%) 7 (2.85%)	68 (30.91%) 130 (59.09%) 14 (6.36%) 1 (0.45%) 7 (3.18%)

3.2.3 Results and conclusions

3.2.3.1 Sponsor's analysis results

The comments and tables below, from the sponsor's report, summarize their results.

Irritation

"Two sets of PP population statistical analyses were performed. The first set (Set 1) did not include 16 subjects who did not have the mild irritant patch applied on Day 10 as required by the protocol. The second set (Set 2) included these 16 subjects in the PP population."

PPP Analysis – Set 1

	Test Placebo Patch	***Mild Irritant Patch***	***Adjusted****	***Upper 95% CI***
Mean Cumulative Irritation (Day 22)	*0.53 ± 0.79 N=225*	*0.88 ± 1.10 N=225*	*1.11 ± 1.37*	*-0.4029*
Total Cumulative Irritation (sum of all visits)	*2.71 ± 3.29 N=225*	*4.23 ± 4.88 N=229*	*5.28 ± 6.10*	*-1.817*
**Mild irritant patch times 1.25*				

PPP Analysis – Set 2

	Test Placebo Patch	***Mild Irritant Patch***	***Adjusted****	***Upper 95% CI***
Mean Cumulative Irritation (Day 22)	*0.54 ± 0.80 N=239*	*0.89 ± 1.09 N=237*	*1.11 ± 1.36*	*-0.4000*
Total Cumulative Irritation (sum of all visits)	*2.76 ± 3.34 N=239*	*4.39 ± 4.89 N=241*	*5.48 ± 6.11*	*-1.984*
**Mild irritant patch times 1.25*				

"The upper limits of the 95% CI for both the mean cumulative irritation score on Day

22 and the total cumulative irritation score over the entire 21 day period of application were both less than zero, demonstrating non-inferiority of the test placebo patch to the mild irritant patch."

Sensitization

"In the sensitization phase of the study, none of the subjects demonstrated a sensitization response, defined as an irritation score greater than 4 and/or an "other effects" score greater than 2. The maximum irritation score recorded during the sensitization phase was 2 and the maximum "other effects" score was 0."

3.2.3.2 Reviewer's results

A) Irritation study

Remark: Last observation carried forward (LOCF) was used for 5 subjects ([redacted] (b) (6) [redacted] (b) (6)) for mild irritant group based on FDA clinical reviewer's comments.

Primary endpoint: Mean Cumulative Irritation scores

Table 3 presents the frequency of irritation scores for each treatment. Frequency of mean cumulative irritation scores per each patch application is shown in Table 4.

Table 3: Frequency of irritation scores (IRRFPP)

Visit Day	Treatment	Score					
		0	1	2	3	4	6
Day 4	Test placebo	171	44	25			
	Mild irritant	164	45	17	1	1	
Day 7	Test placebo	180	48	12			
	Mild irritant	156	48	23	1		
Day 10	Test placebo	173	45	22			
	Mild irritant	140	55	27	2	3	1
Day 13	Test placebo	187	43	10			
	Mild irritant	152	52	20	3		1
Day 16	Test placebo	173	54	13			
	Mild irritant	148	44	29	3	3	1
Day 19	Test placebo	163	60	17			
	Mild irritant	135	50	34	4	4	1
Day 22	Test placebo	155	60	25			
	Mild irritant	116	69	30	8	4	1

Table 4: Frequency of maximum total irritation scores per each patch *per subject*

	0	1	2	3	4	6	Total
Test placebo	97	85	58				240
Mild irritant	71	80	60	11	5	1	228

Table 5: Frequency of mean cumulative irritation scores (IRRFPP)

	0	>0, <0.5	=0.5, <1	=1, <1 5	=1.5, <2	2	3	Total
Test placebo	97	75	35	27	4	2		240
Mild irritant	71	67	37	30	15	1	7	228

Table 6: Analysis of the mean cumulative irritation scores using mixed model (IRRFPP)

Test placebo (LS mean μ_{TP})	Mild irritant (LS mean μ_{MI})	Upper limit one-sided 95% CB (μ_{TP} -1.25μ_{MI})	Pass the Non-inferiority test
0.3917	0.5482	-0.2323	Yes

Non-inferiority analyses based on the mean cumulative irritation scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference (μ_{TP} -1.25μ_{MI}) was less than zero and the non-inferiority test was passed for test placebo patch versus mild irritant patch. Therefore, the irritation potential of the test placebo patch is not worse than that of the mild irritant patch.

Secondary endpoints: dichotomized variables

Secondary endpoints examined included the dichotomized mean cumulative irritation scores and irritation scores per study day. Analyses of these endpoints are discussed below.

Dichotomized Mean Cumulative Irritation Scores

Remark: Two hundred and twenty (222) subjects out of the 246 in the IRRFPP were included in the dichotomized analysis since this analysis required the subject had scores for both test placebo and mild irritant patches.

In addition to the primary endpoint analyses, analyses for the secondary endpoints were conducted to compare the test placebo and mild irritant with regard to the proportion of subjects who had mean cumulative irritation score greater than or equal to 1 or 2. Based on the 95% upper confidence bound for the difference in proportions, the test placebo might exceed the mild irritant by at most -2.96% (negative) with regard to the proportion of subjects who had the mean cumulative irritation scores greater than or equal to 1 and at most 0.75% with regard to the proportion of subjects who had the mean cumulative irritation scores greater than or equal to 2. (for these data, the highest UB was obtained from Schuirmann's method.)

Table 7: Analysis of the dichotomized mean cumulative irritation score (IRRFPP)

Critical value (crit)	Score >=crit for Test placebo & not for Mild irritant	Score>=crit for Mild irritant & not for Test placebo	P_{TP} -P_{MI}*	95% Upper Bound# for P_{TP} -P_{MI}		
				McNemar	Clopper	Schuirmann
1	8	25	-0.0766	-0.0304	-0.0494	**-0.0296**
2	1	4	-0.0135	0.0075	-0.0037	**0.0075**

Note: There are 222 subjects who had both patches (Test and Mild irritant).
*: p_{TP}=P (mean cumulative irritation score greater than/equal to crit for test placebo), and p_{MI}=P (mean cumulative irritation score greater than/equal to crit for mild irritant).
#: The highest upper bound is marked in bold.

Dichotomized Irritation Scores per Visit Day

Based on the 95% upper confidence bound for the difference in proportions, the test placebo might exceed the mild irritant by at most 7.99 percentage points at Day 4 with regard to the proportion of subjects who had irritation scores greater than or equal to 1. Also, the test placebo might exceed the mild irritant by at most 7.14 percentage points at Day 4 with regard to the proportion of subjects who had irritation scores greater than or equal to 2.

Table 8: Analysis of the dichotomized irritation score for each visit (IRRFPP)

Critical value (crit) Visit	Score >=crit for Test placebo & not for Mild irritant	Score>=crit for Mild irritant & not for Test placebo	P_{TP} -P_{MI}*	95% Upper Bound# for P_{TP} -P_{MI}		
				McNemar	Clopper	Schuirmann
Crit=1						
Day 4	25	19	0.0270	0.0806	0.0526	**0.0799**
Day 7	17	29	-0.0541	0.0004	-0.0315	**0.0007**
Day 10	8	30	-0.0991	-0.0502	-0.0680	**-0.0492**
Day 13	14	34	-0.0901	-0.0352	-0.0605	**-0.0344**
Day 16	16	28	-0.0541	-0.0008	-0.0315	**-0.0004**
Day 19	18	31	-0.0586	-0.0026	-0.0350	**-0.0022**
Day 22	18	46	-0.1261	-0.0640	-0.0911	**-0.0627**
Crit=2						
Day 4	15	8	0.0315	**0.0714**	0.0584	0.0707
Day 7	6	17	-0.0496	-0.0099	-0.0280	**-0.0096**
Day 10	7	19	-0.0541	-0.0122	-0.0315	**-0.0117**
Day 13	5	16	-0.0496	-0.0115	-0.0280	**-0.0111**
Day 16	3	25	-0.0991	-0.0569	-0.0680	**-0.0559**
Day 19	6	28	-0.0991	-0.0528	-0.0680	**-0.0516**
Day 22	7	22	-0.0676	-0.0239	-0.0421	**-0.0232**

Note: There are 222 subjects who had both patches (Test and Mild irritant).
*: p_{TP}=P (irritation score greater than/equal to crit for test placebo), and p_{MI}=P (irritation score greater than/equal to crit for mild irritant).
#: The highest upper bound is marked in bold.

B) Sensitization study

Table 9 presents the frequency of irritation scores for the challenge period for the Sensitization Per-Protocol population (SNSFPP).

Table 9: Frequency of irritation scores for the challenge period (SNSFPP)

Evaluation Day	0	1	2	Total N
30 min	159	47	14	220
24 hours	190	27	2	219*
48 hours	214	3	1@	218*
72 hours	218		1@	219*

*: Irritation scores were missed for subject (b) (6) at hour 24, 1077 and (b) (6) at hour 48, and (b) (6) at hour 72.
@: Subject (b) (6) had irritation scores 2 at 0.5, 24, 48, and 72 Hours.

Three subjects missed irritation scores at 24, 48, 72 hours.

Subject number	30 minutes	24 hours	48 hours	72 hours
(b) (6)	1	0		0
	0		0	0
	0	0		

Remark: Subject (b) (6) for test placebo patch had the irritation scores: 2 (Day 4), 1 (Day 7), 1 (Day 10), 0 (Day 13), 1 (Day 16), 2 (Day 19), 2 (Day 22) in the induction phase, and, 2 (0.5 hour), 2 (24 hours), 2 (48 hours), and 2 (72 hours) in the challenge phase.

FDA clinical reviewer pointed: "*Using the sensitization definition previously provided, one subject* (b) (6) *appears to have had a potential sensitization reaction. Subject* (b) (6) *had an irritation score of 2 that persisted from 30 min to 72 hour post challenge patch removal. However, this subject presented the same reaction after the first and last applications of the placebo test patch during the induction phase. Therefore, this subject is deemed to have had an irritation reaction and not a sensitization reaction."*

No subject should be considered to be potentially sensitized for the test placebo patch.

3.3 Protocol #PRG-604: Evaluation of adhesion

3.3.1 Study design and endpoints

Study Objective

The primary objective was to compare the bioequivalence of an investigational scopolamine transdermal patch, releasing approximately 1.0 mg scopolamine over three days (72 hours), versus the reference product, TransdermScop®. The secondary objective was to evaluate the safety, tolerability and adhesion of the transdermal patches. In this review we focus on the evaluation of adhesion.

Study design

This was a single site, open-label, randomized, two-way crossover pharmacokinetic study conducted on 30 healthy adult subjects (15 males and 15 females) under fasting conditions. A total of 28 subjects (13 males and 15 females) completed the clinical phase of the study.

On the morning of Day 1 for each period (Period 1: 9/18/2006 and Period 2: 9/25/2006), subjects received a single scopolamine transdermal system delivering 1.0 mg over three days. Patch applications were separated by a washout period of 7 days. Patch adhesion was evaluated within 10 minutes of each vital sign determination (i.e., every 12 hours) and within 10 minutes prior to patch removal during the wear period.

FDA reviewer comments: *According to the* Draft Guidance on Scopolamine Film, Extended Release/Transdermal, 1 mg/72 hr (October 2011), *the recommended frequency for adhesion evaluation is "at least daily". Thus, the sponsor's adhesion evaluation of every 12 hours is acceptable.*

Treatments

Treatment	Description
Product A (Test)	Scopolamine Transdermal System 1.31 mg, 2.5 cm^2 Manufactured by: Aveva DDS, Inc.* Lot No.: 35409 Manufactured date: 07/26/06 (b) (4)
Product B (Reference)	TransdermScop®, 1.5 mg Manufactured by: ALZA Corporation. Distributed by: Novartis Consumer Health, Inc. Lot No.: 0526942** Expiration date: 08/08

* The drug product manufacturer is Aveva Drug Delivery Systems, Inc.
** bulk product Lot #20711701 as per Certificate of Conformance

Adhesion evaluations

0 =	90% 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 =	patch detached (patch completely off the skin)

Clinical endpoints

Primary endpoint: Mean Cumulative Adhesion Scores

The mean cumulative adhesion scores were obtained by adding total observations in the application period and dividing by the number of observations.

Secondary endpoints: The clinical reviewer requested a comparator of test versus reference with regard to the proportion of patch applications with meaningful detachment. Two dichotomized endpoints, defined as more than or equal score 1 (≥10% detached) and more than or equal score 2 (≥25% detached), were analyzed for the adhesion mean and scores at six scoring times.

3.3.2 Subject disposition

A total of 30 healthy adult subjects were enrolled and included in the sponsor's Per Protocol (ADHPP) and FDA's Per Protocol (ADHFPP) populations for adhesion analysis. However, Subject No. (b) (6) was withdrawn by the Investigator due to adverse events after completion of Period 1 (Reference) and therefore was missing all adhesion scores for test treatment in period 2. There were 29 subjects in the test group and 30 subjects in the reference group for ADHPP and ADHFPP.

Table 10: Demographic characteristics (ADHFPP)

	Test (N=29)	Reference (N=30)
Age (years)		
Mean (Range)	40.66 (24-55)	40.7 (24-55)
Gender		
Female Male	15 (51.72%) 14 (48.28%)	15 (50%) 15 (50%)
Race		
White Black/African American	28 (96.55%) 1 (3.45%)	29 (96.67%) 1 (3.33%)

3.3.3 Results and conclusions

3.3.3.1 Sponsor's analysis results

The sponsor concluded the test patch is non-inferiority to the reference patch based on their analysis below.

"The non-inferiority of the test product relative to the reference product was assessed with respect to % Adhesion (1-(Adhesion Sum)/24).

An ANOVA was performed on ln-transformed %Adhesion. The ANOVA model included sequence,formulation and period as fixed effects and subject nested within sequence as a random effect. Sequence was tested using subject nested within sequence as the error term. Each ANOVA included calculations of LSM, the difference between formulation LSM and the standard error associated with this difference. The above statistical analyses were performed using the SAS® GLM (version 8.2) procedure.

The lower bound of a one-sided 95% confidence interval on the ratio of geometric means was calculated by constructing first on the log scale a confidence interval on the difference of least squares means (LSM), and then transforming the endpoints by anti-logarithm back to the original scale. The determination of non-inferiority was based on whether the lower limits of the confidence interval for the ratio of LSM (expressed in %) was greater than 80%."

"Ninety percent of the subjects or more obtained adherence scores of 0 (90% adhered) or 1 (75% to less than 90% adhered) following treatment with the Aveva patch and TransdermScop®, regardless of time points. The ratio of LSM of the Aveva patch over TransdermScop® for the % adhesion was 97%, 0.8687 (test) versus 0.8961 (reference) with a lower 95% confidence interval limit of 91%."

3.3.3.2 Reviewer's results

The analysis is based on FDA's Per Protocol population and follows the guidance-recommended approach. The FDA statistical reviewer did not repeat the sponsor's analysis for this patch study.

FDA clinical reviewer comments: *"For Subject 3, the Reference patch fell off prior to the 36-hour evaluation time. A score of 4 is recorded for the 36-hour and 48-hour evaluation times.*

However, scores are not recorded for the 60-hour and 72-hour evaluation times. A score of 4 should be carried forward for these two evaluation times."

The frequency of cumulative adhesion scores per each patch at each evaluation day is shown in Table 11.

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 (b) (6) reference patch fell off after Hour 48. A score 4 at Hour 48 was carried forward to Hour 60 and 72.

Primary endpoint: Mean cumulative adhesion score

The frequency of mean cumulative adhesion scores per each patch is shown in Table 12. The mean cumulative adhesion scores were analyzed using a mixed model and are presented in Table 13.

Table 12: Frequency of mean cumulative adhesion scores

Mean	0	0.167	0.333	0.5	0.667	0.8333	1	1.667	2	2.167	2.667
Test	3	6	11	3	2	1		1	1	1	
Reference	2	7	9	3	3	3	2				1

Table 13: Analysis for the mean cumulative adhesion scores using mixed model

Test (Ls mean)	Reference (Ls mean)	Upper limit one-sided 95%CB (test-1.25ref)	Pass the Non-inferiority test
0.4711	0.4944	0.1059	No

Non-inferiority analyses based on the mean cumulative adhesion scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference (μ_T -1.25μ_R) was larger than zero and the non-inferiority test was failed for test versus reference patch. Therefore, the adhesion potential of the test is worse than that of the reference.[3]

[3] The adhesion potential of test is also worse than that of the reference for the adhesion scores without LOCF or subject (b) (6)

Secondary endpoint: Dichotomized adhesion scores

Remark: Twenty-nine (29) subjects were included in the dichotomized analysis since the analysis required the subject had both scores, for test and reference patches.

Table 14: Analysis of the dichotomized adhesion score

Visit Hour	Score >=crit for Test & not for Reference	Score >=crit for Reference & not for Test	$P_T - P_R$ *	95% Upper Bound# for $P_T - P_R$		
Crit=1				McNemar	Clopper	Schuirmann
Mean	2	2	0.000	**0.148**	0.098	0.1407
12	7	4	0.103	**0.323**	0.246	0.3019
24	10	8	0.069	**0.343**	0.202	0.3230
36	5	5	0.000	**0.214**	0.098	0.2028
48	6	12	-0.207	0.060	-0.086	**0.0674**
60	4	5	-0.034	**0.170**	-0.002	0.1628
72	7	5	0.069	**0.299**	0.202	0.2803
Crit=2						
Mean	2	1	0.034	0.167	0.153	**0.1885**
12	1	0	0.034	0.125	0.153	**0.1885**
24	2	0	0.069	0.181	0.202	**0.2325**
36	3	1	0.069	0.215	0.202	**0.2325**
48	1	2	-0.034	**0.098**	-0.002	0.094
60	1	2	-0.034	**0.098**	-0.002	0.094
72	2	2	0.000	**0.148**	0.098	0.1407

Note: Subject (b) (6) was excluded from the analysis of the dichotomized adhesion scores.
*: p_T=P (mean cumulative/daily adhesion score greater than/equal crit for test), and p_R=P (mean cumulative/daily adhesion score greater than/equal crit for reference).
#: The highest upper bound is marked in bold.

In addition to the primary endpoint analyses, analyses for the secondary endpoints were conducted to compare the test and reference with regard to the proportion of subjects who had mean and visit adhesion scores greater than or equal to 1 (≥10% detached) and who had mean and visit adhesion scores greater than or equal to 2 (≥25% detached).

Based on the 95% upper confidence bound for the difference in proportions for mean and by-visit scores, the test might exceed the reference by at most 14.8 percentage points with regard to the proportion of subjects who had mean adhesion scores greater than or equal to 1 and at most 18.9 percentage points with regard to the proportion of subjects who had mean adhesion scores greater than or equal to 2. Also the test might exceed the reference by at most 34.3 percentage points at hour 24 with regard to the proportion of subjects who had daily adhesion scores greater than or equal to 1 and at most or 23.3 percentage points at hour 24 and 36 with regard to the proportion of subjects who had daily adhesion scores greater than or equal to 2.

4 SUMMMARY AND CONCLUSIONS

4.1 Statistical Issues and Findings

Irritation and sensitization study (Protocol PRG-603)

Irritation

Primary endpoint: Mean cumulative irritation scores were analyzed. Mean cumulative irritation scores were 0.3917 for test placebo patch and 0.5482 for mild irritant patch. The non-inferiority criterion was satisfied for test patch versus reference patch, implying that we can conclude that the population mean of the cumulative irritation for the test placebo patch does not exceed that of the mild irritant patch by more than 25% (i.e. $\mu_{TP} / \mu_{MI} \leq 1.25$).

Secondary endpoints: Dichotomized endpoints for mean cumulative irritation scores were considered for the secondary analyses. Based on the 95% upper confidence bound for the difference in proportions, the test placebo might exceed the mild irritant by at most -2.96 (negative) percentage points with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 1. And also the test placebo might exceed the mild irritant by at most 0.75 percentage points with regard to the proportion of subjects who had mean cumulative irritation scores greater than or equal to 2.

The test placebo and mild irritant patches were compared with regard to the proportion of product applications with irritation scores greater than or equal to 1 or to 2 for each study day (Day 4, 7, 10, 13, 16, 19, and 22). The test placebo might exceed the mild irritant by at most 7.99 percentage points at Day 4 based on scores greater than or equal to 1. And also the test placebo might exceed the mild irritant by at most 7.14 percentage points at Day 4 based on scores greater than or equal to 2.

Sensitization

No subject was identified to be potentially sensitized to the test placebo patch. There was no reference product in the challenge phase for this study.

Adhesion study (Protocol PRG-604)

Primary endpoint: The mean cumulative adhesion scores were analyzed using a mixed linear model. Non-inferiority analyses based on the mean cumulative adhesion scores (primary endpoint) showed that the one-sided 95% upper CB for the adjusted mean difference (μ_T -1.25μ_R) was larger than zero (0.1059) and the non-inferiority test was failed for test versus reference patch. Therefore, the adhesion potential of the test is worse than that of the reference.

Secondary endpoints: Based on the 95% upper confidence bound for the difference in proportions for adhesion scores, the test might exceed the reference by at most 14.8 and 34.3 percentage points with regard to the proportion of subjects who had mean or daily adhesion scores at hour 24 greater than or equal to 1 (>=10% detached). Also the test might exceed the reference by at most 18.9 and 23.3 percentage points with regard to the proportion of subjects who had mean or daily adhesion scores at hour 24 and 36 greater than or equal to 2 (>= 25% detached).

Main difference between sponsor's results and our results:

Where the sponsor's results differ from our results, mainly it is due to the following reasons.

a) The FDA's Irritation Per Protocol population (IRRFPP) and Sensitization Per Protocol population (SENFPP) were not the same as the sponsor's, IRRPPP and SENPPP populations.
b) FDA and sponsor used different scoring conversions for the other effect scores for irritation scores. The differences between those populations are listed in the Table 1: Patient disposition.
c) The sponsor analyzed the score at Day 22 and total irritation score per each patch per subject using the mixed model-test placebo patch versus mild irritant patch. Our analysis used only the mean of total irritation scores per each patch per subject.
d) The sponsor carried out non-standard, statistical analyses for the adhesion study. We did not repeat their analysis.

4.2 Conclusions

The test placebo patch was found to be non-inferior to the mild irritant patch for irritation. No subject was considered to be potentially sensitized for the test placebo patch. The adhesion potential of the test patch is worse than that of the reference patch.

_____
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/s/

HUAIXIANG LI
03/13/2013

STELLA C GROSSER
03/18/2013

STELLA G MACHADO
03/22/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78830

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-830
Drug Product Name	Scopolamine Transdermal System
Strength(s)	1 mg/72 hr
Applicant Name	Perrigo R&D Company
Address	515 Eastern Ave. Allegan, MI 49010
Applicant's Point of Contact	Valerie Gallagher Associate Director, NDA/ANDA Regulatory Affairs
Contact's Telephone Number	269-673-8451
Contact's Fax Number	269-673-7655
Original Submission Date(s)	February 23, 2007
Submission Date(s) of Amendment(s) Under Review	September 20, 2007 (Bioequivalence amendment; previously reviewed) March 10, 2008 (Bioequivalence amendment, previously reviewed) December 11, 2008(Bioequivalence amendment)
Reviewer	Zhuojun Zhao, Ph.D.
Study Number (s)	AA31201
Study Type (s)	Fasting Bioequivalence
Strength (s)	1 mg/72 hr
Clinical Site	MDS Pharma Services
Clinical Site Address	2350 Cohen Street, Saint-Laurent, Montreal, Quebec, H4R 2N6, Canada
Analytical Site	(b) (4)
Analytical Site Address	
OUTCOME DECISION	**Acceptable**

Review of an Amendment

1 EXECUTIVE SUMMARY

Perrigo R & D Company submitted the first generic application for Scopolamine Transdermal System, 1 mg/72 hr on February 2007. This application contained the results of a fasting bioequivalence (BE) study comparing the test product to the corresponding reference product, TransdermScop®, 1 mg/ 72 hr. The BE study was designed as a single site, open label, randomized, single dose, two-way crossover study in healthy male and female subjects. The firm's fasting study was found acceptable but the application was found incomplete due to incomplete dissolution. The firm submitted an amendment to provide dissolution data including individual data of drug release for the test and reference products for 12 units on 20 September, 2007. The firm conducted acceptable comparative dissolution testing on all strengths using the FDA-recommended dissolution

method. However, the specifications as proposed by the firm were found to be unacceptable based on the data submitted and DBE had recommended different dissolution specifications. The firm was asked to acknowledge the acceptance of the specifications as recommended by the DBE in the deficiency letter dated November 30, 2007.

On 10 March, 2008, the firm submitted an amendment providing additional dissolution testing data on an exhibit and packaging batch of its test product. The DBE acknowledged the firm's submission of the additional dissolution data using the FDA recommended method. Based on the data, the firm's proposed specifications for its test product were found acceptable. However, the dissolution testing was still incomplete. The firm was requested to provide comparative dissolution testing in at least three additional dissolution media (i.e., pH 1.2, 4.5, and 6.8 buffer) to demonstrate the effect of potential dose dumping in the deficiency letter dated June 30, 2008.

In the current amendment dated December 11, 2008, Perrigo R & D Company submitted the in vitro dissolution testing data on 12 dosage units in five different pH media (pH 1.2, 4.5, 6.8, 7.5 buffers and water) for both the test and reference products. The data showed no evidence of dose dumping. The firm's response to the deficiency is acceptable.

The application is acceptable with no deficiencies.

2 RESPONSE TO DEFICIENCIES

DBE Deficiency #1:

We acknowledge that you have submitted additional dissolution data using the FDA-recommended dissolution method. However, your dissolution testing is still incomplete. Please submit comparative in vitro dissolution testing on 12 dosage units of the test and reference products in at least three different pH media (i.e., pH 1.2, 4.5 and 6.8 buffers). Agitation speed may have to be increased if appropriate. It is acceptable to add a small of surfactant, if necessary. Please conduct dissolution testing until at least 80% of the labeled amount of the drug is released. Also, if possible, the dissolution testing should be conducted on your biostudy lots of the test and reference products.

Please submit the comparative dissolution results which should include the individual dosage unit data as well as the mean, range, %CV at each time point for the 12 dosage units tested, and dates of dissolution testing. In addition, please submit the dissolution testing data summary table (Table 5) with the above data. More information on the electronic Common Technical Document (eCTD) format for BE summary tables are provided on http://www. fda.gov/cder/ogd/DBE_tables.pdf.

Firm's Response:

Perrigo acknowledges that the individual unit dissolution results were omitted for the different media, and would like to apologize for any inconvenience this omission my have caused. The in vitro dissolution testing has been performed on 12 dosage units in

five different pH media (pH 1.2, 4.5, 6.8, 7.5 buffers and water) for both the test and reference products. To obtain 80% of label claim release, the dipping speed was increased to 60 dpm for all testing, and an additional time point of 96 hours was included. The use of a surfactant was not feasible due to the low volume of media (20 mL) and that the reciprocating dipping action would cause an excess of foam. The stability of scopolamine base in the buffer solutions and confirmation of sink conditions for scopolamine base were evaluated prior to conducting the testing. The results for the additional drug release testing have now been included in Module 3 section 3.2.P.2.2.1.3, in vitro Data Comparison.

The dissolution summary table (Table 5) has also been updated and included in Module 5 section 5.2 Tabular Listing.

Reviewer's Comment:
Based on the submitted data, the dissolution testing using five different pH media (pH 1.2, 4.5, 6.8, 7.5 buffers and water), for the test product in comparison with Reference Listed Drug (RLD) product are acceptable. The data showed no evidence of dose dumping. The dissolution testing was conducted on the same lot of the test product used in the firm's bioequivalence study. The firm's response to the deficiency is acceptable. The dissolution summary data follows.

3 DISSOLUTION DATA

Table 1. In Vitro Dissolution in Water

Dissolution Conditions	**Apparatus:**	Apparatus 7 (reciprocating disks)
	Speed of Rotation:	(b) (4)
	Medium:	Distilled water
	Volume:	20 mL
	Temperature:	32.0 ± 0.3°C
	Stroke depth:	2 - 3 cm
	Dipping speed:	(b) (4)
Firm's Proposed Specifications	See Below	
Dissolution Testing Site (Name, Address)	Aveva Drug Delivery Systems, (b) (4) 3250 Commerce Parkway, Miramar, FL 33025	

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**							**Study Report Location**
				1 hr	**2 hrs**	**4 hrs**	**6 hrs**	**24 hrs**	**48 hrs**	**72 hrs**	
Perrigo Exhibit Batch: Scopolamine Transdermal Therapeutic System Lot # 35409, July 26, 2006	Transdermal Film, Extended Release – 1 mg/72 hr	12	Mean	41	44	48	50	69	91	105	Module 3, 3.2.P.2.2.1.3
			RSD (%)	4.7	2.2	1.9	2.1	3.6	4.2	3.8	
RLD: Transderm Scōp® Lot # 20711701, Exp 08/2008	Transdermal Film, Extended Release – 1 mg/72 hr	12	Mean	28	35	40	43	63	85	105	Module 3, 3.2.P.2.2.1.3
			RSD (%)	6.1	3.6	2	1.8	1.6	1.5	1.5	
Firm's Proposed Specifications				(b) (4)							

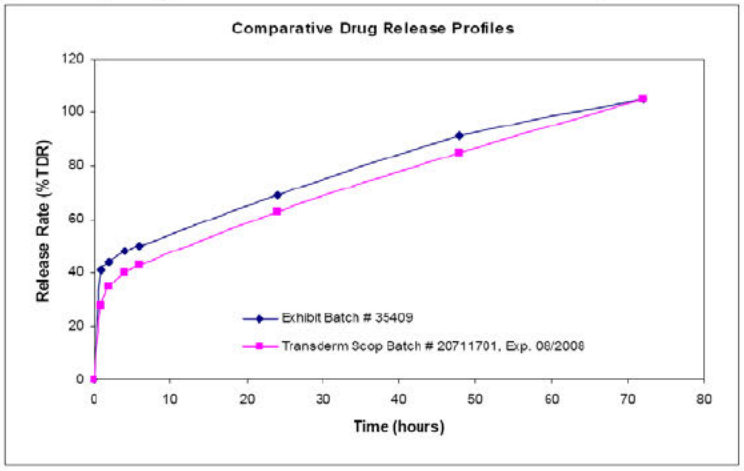


Table 2 In Vitro Dissolution in Dissolution Medium 1: pH 1.2 Buffer

Dissolution Conditions	**Apparatus:**	Apparatus 7 (reciprocating disks)
	Speed of Rotation:	(b) (4)
	Medium:	(b) (4) Acid Buffer, pH 1.2
	Volume:	20 mL
	Temperature:	32.0 ± 0.3°C
	Stroke depth:	2 - 3 cm
	Dipping speed:	(b) (4)
	Reference:	
	Testing Dates:	09/15/08 – 09/24/08
Firm's Proposed Specifications	See Below	
Dissolution Testing Site (Name, Address)	Aveva Drug Delivery Systems, (b) (4) 3250 Commerce Parkway, Miramar, FL 33025	

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times** 6 hrs	24 hrs	48 hrs	72 hrs	96 hrs
Perrigo Exhibit Batch: Scopolamine Transdermal Therapeutic System Lot # 35409, July 26, 2006	Transdermal Film, Extended Release – 1 mg/72 hr	12	Mean	51	69	82	87	90
			RSD (%)	3.6	5.9	5.8	4.8	3.9
RLD: Transderm Scōp® Batch #22614001, Exp. 09/2010	Transdermal Film, Extended Release – 1 mg/72 hr	12	Mean	27	39	54	67	79
			RSD (%)	2.5	1.8	1.7	1.9	1.9
Firm's Proposed Specifications				(b) (4)				

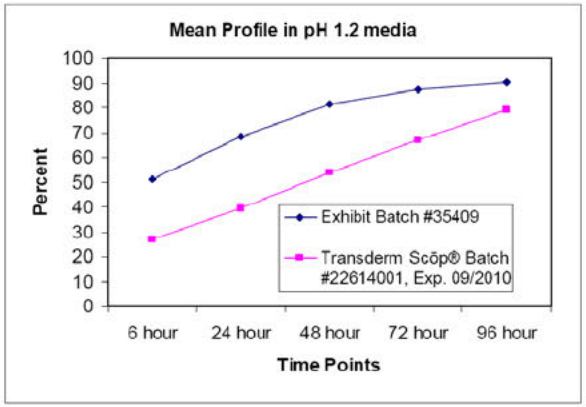


Table 3. In Vitro Dissolution in Dissolution Medium 2: pH 4.5 Buffer

Dissolution Conditions	**Apparatus:**	Apparatus 7 (reciprocating disks)
	Speed of Rotation:	(b) (4)
	Medium:	Acetate Buffer, pH 4.5
	Volume:	20 mL
	Temperature:	32.0 ± 0.3°C
	Stroke depth:	2 - 3 cm
	Dipping speed:	(b) (4)
	Reference:	
	Testing Dates:	09/22/08 – 09/30/08
Firm's Proposed Specifications	See Below	
Dissolution Testing Site (Name, Address)	Aveva Drug Delivery Systems, (b) (4) 3250 Commerce Parkway, Miramar, FL 33025	

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times** 6 hrs	24 hrs	48 hrs	72 hrs	96 hrs
Perrigo Exhibit Batch: Scopolamine Transdermal Therapeutic System Lot # 35409, July 26, 2006	Transdermal Film, Extended Release – 1 mg/72 hr	12	Mean	48	59	72	79	83
			RSD (%)	8.7	7.5	6.7	5.8	4.8
RLD: Transderm Scōp® Batch #22614001, Exp. 09/2010	Transdermal Film, Extended Release – 1 mg/72 hr	12	Mean	24	33	42	52	61
			RSD (%)	2.6	1.9	2.0	1.5	1.2
Firm's Proposed Specifications								(b) (4)

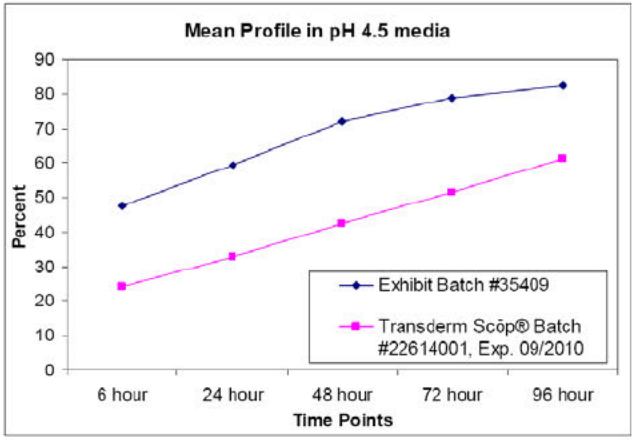


Table 4. In Vitro Dissolution in Dissolution Medium 3: pH 6.8 Buffer

Dissolution Conditions	**Apparatus:**	Apparatus 7 (reciprocating disks)
	Speed of Rotation:	(b) (4)
	Medium:	Phosphate Buffer, pH 6.8
	Volume:	20 mL
	Temperature:	32.0 ± 0.3°C
	Stroke depth:	2 - 3 cm
	Dipping speed:	(b) (4)
	Reference:	
	Testing Dates:	11/10/08 – 11/17/08
Firm's Proposed Specifications	See Below	
Dissolution Testing Site (Name, Address)	Aveva Drug Delivery Systems, (b) (4) 3250 Commerce Parkway, Miramar, FL 33025	

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times** 6 hrs	24 hrs	48 hrs	72 hrs	96 hrs
Perrigo Exhibit Batch: Scopolamine Transdermal Therapeutic System Lot # 35409, July 26, 2006	Transdermal Film, Extended Release – 1 mg/72 hr	12	Mean	48	64	82	90	92
			RSD (%)	6.8	5.9	4.9	4.1	3.4
RLD: Transderm Scōp® Batch #22614001, Exp. 09/2010	Transdermal Film, Extended Release – 1 mg/72 hr	12	Mean	28	41	56	69	81
			RSD (%)	2.2	1.5	1.2	1.1	1.2
Firm's Proposed Specifications								(b) (4)

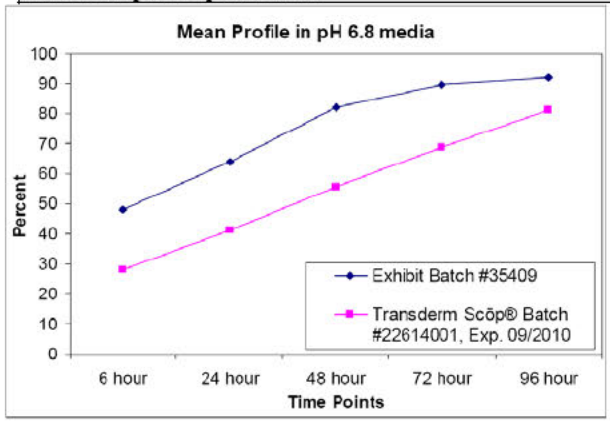


Table 5. In Vitro Dissolution in Dissolution Medium 4: pH 7.5 Buffer

Dissolution Conditions	**Apparatus:**	Apparatus 7 (reciprocating disks)
	Speed of Rotation:	(b) (4)
	Medium:	Phosphate Buffer, pH 7.5
	Volume:	20 mL
	Temperature:	32.0 ± 0.3°C
	Stroke depth:	2 - 3 cm
	Dipping speed:	(b) (4)
	Reference:	
	Testing Dates:	10/13/08 – 10/20/08
Firm's Proposed Specifications	See Below	
Dissolution Testing Site (Name, Address)	Aveva Drug Delivery Systems, (b) (4) 3250 Commerce Parkway, Miramar, FL 33025	

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times** 6 hrs	24 hrs	48 hrs	72 hrs	96 hrs
Perrigo Exhibit Batch: Scopolamine Transdermal Therapeutic System Lot # 35409, July 26, 2006	Transdermal Film, Extended Release – 1 mg/72 hr	12	Mean	44	59	76	85	88
			RSD (%)	5.2	4.1	6.3	5.5	4.5
RLD: Transderm Scōp® Batch #22614001, Exp. 09/2010	Transdermal Film, Extended Release – 1 mg/72 hr	12	Mean	27	40	54	67	80
			RSD (%)	2.1	2.2	2.4	2.5	2.9
Firm's Proposed Specifications								(b) (4)

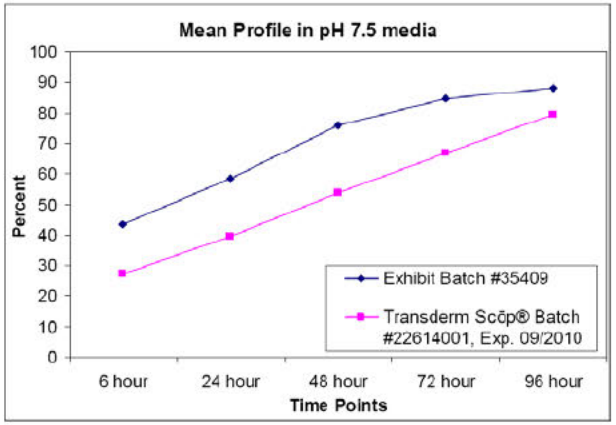
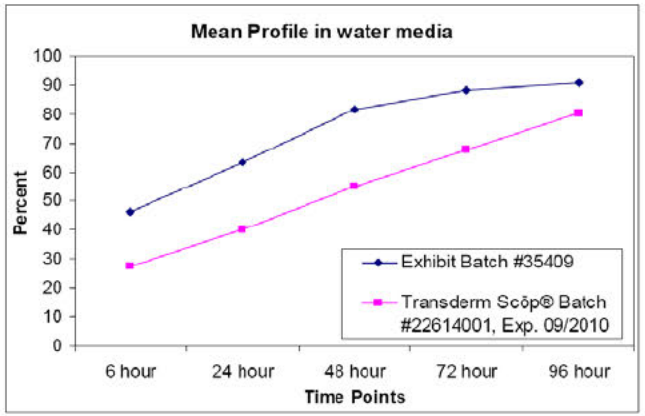


Table 5. In Vitro Dissolution in Dissolution Medium 5: Water

Dissolution Conditions	**Apparatus:**	Apparatus 7 (reciprocating disks)
	Speed of Rotation:	(b) (4)
	Medium:	USP Purified Water
	Volume:	20 mL
	Temperature:	32.0 ± 0.3°C
	Stroke depth:	2 - 3 cm
	Dipping speed:	(b) (4)
	Reference:	
	Testing Dates:	11/17/08 – 11/24/08
Firm's Proposed Specifications	See Below	
Dissolution Testing Site (Name, Address)	Aveva Drug Delivery Systems, (b) (4) 3250 Commerce Parkway, Miramar, FL 33025	

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times** 6 hrs	24 hrs	48 hrs	72 hrs	96 hrs
Perrigo Exhibit Batch: Scopolamine Transdermal Therapeutic System Lot # 35409, July 26, 2006	Transdermal Film, Extended Release – 1 mg/72 hr	12	Mean	46	63	82	88	91
			RSD (%)	8.2	6.5	4.9	3.4	2.4
RLD: Transderm Scōp® Batch #22614001, Exp. 09/2010	Transdermal Film, Extended Release – 1 mg/72 hr	12	Mean	28	40	55	68	80
			RSD (%)	2.3	1.8	1.5	1.6	1.8
Firm's Proposed Specifications								(b) (4)



4 COMMENTS

The firm's responses to the deficiencies in the current amendment are considered complete. The firm submitted the in vitro dissolution testing data on 12 dosage units in five different pH media (pH 1.2, 4.5, 6.8, 7.5 buffers and water) for both the test and reference products. The dissolution testing was conducted on the same lot of the test product used in the firm's bioequivalence study. Although the firm's dissolution data across media does show higher amounts released (compared to that of the RLD), the relative shape of the profiles are similar. Furthermore, the test data showed no evidence of dose dumping. The firm's response to the deficiency is acceptable.

5 RECOMMENDATIONS

The dissolution testing conducted by Perrigo R&D Company on its Scopolamine Transdermal System, 1 mg/72 hr (Lot # 35409), comparing it to Alza Corporation's TransdermScop®, 1 mg/72 hr is acceptable.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-830

APPLICANT: Perrigo R&D Company

DRUG PRODUCT: Scopolamine Transdermal System

The Division of Bioequivalence has completed its review and has no further questions at this time.

We concur with your dissolution testing method and specifications as follows:

The dissolution testing should be conducted using the FDA-recommended method of 25 x 150 mm test tubes containing 20 mL of distilled water at 32°C ± 0.3°C using USP Apparatus 7 (reciprocating disk) at a stroke of 2-3 cm at a rate of 30-60 cycles/minute. The test product should meet the following specifications:

6 hr: (b) (4) %
24 hr: (b) (4) %
48 hr: (b) (4) %
72 hr: (b) (4) %

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}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

5.1 Outcome Page

ANDA: 78-830

Enter Review Productivity and Generate Report

Reviewer: Zhao, Joan **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Scopolamine Transdermal System

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
7153	12/11/2008	Other	Study Amendment	1	1
				Bean Total:	1

Division of Bioequivalence 2 Review Complexity Summary

Study Amendment (s)	
Study Amendment	1
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/

Joan Zhao
1/6/2009 04:58:02 PM
BIOPHARMACEUTICS

Paul Seo
1/7/2009 12:24:37 PM
BIOPHARMACEUTICS

Barbara Davit
1/16/2009 06:58:49 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78830		
Drug Product Name	Scopolamine Transdermal System		
Strength(s)	1 mg/72 hr		
Applicant Name	Perrigo R&D Company		
Address	515 Eastern Ave. Allegan, MI 49010		
Applicant's Point of Contact	Diane L. Morgan		
Contact's Telephone Number	269-686-1729		
Contact's Fax Number	269-673-7655		
Original Submission Date(s)	February 23, 2007		
Submission Date(s) of Amendment(s) Under Review	September 20, 2007 (Bioequivalence amendment; previously reviewed) March 10, 2008 (Bioequivalence amendment)		
Reviewer	Haritha Mandula, Ph.D.		
Study Number (s)	AA31201		
Study Type (s)	Fasting Bioequivalence		
Strength (s)	1 mg/72 hr		
Clinical Site	MDS Pharma Services		
Clinical Site Address	2350 Cohen Street, Saint-Laurent, Montreal, Quebec, H4R 2N6, Canada		
Analytical Site	(b) (4)		
Analytical Site Address			
OUTCOME DECISION	**INCOMPLETE**		

Review of an Amendment

1 EXCECUTIVE SUMMARY

On 10 March, 2008, the firm, Perrigo R & D Company, submitted an amendment to its application for the **first generic product** of Scopolamine Transdermal System, 1 mg/72 hr. The amendment is in response to the deficiency letter sent to the firm dated 30 Nov 2007 (received 03 Dec 2007) by the Division of Bioequivalence (DBE) in which the firm was requested to acknowledge the DBE-recommended specifications for its test product.

The dissolution testing should be conducted in 25 x 150 mm test tubes containing 20 mL of distilled water at 32ºC ± 0.3ºC using USP apparatus 7 (reciprocating disk) at a stroke of 2-3 cm at a rate of 30-60 cycles/minute.

The DBE -recommended specifications are as follows:

6 hr: (b) (4) %
24 hr: (b) (4) %
48 hr: (b) (4) %
72 hr: (b) (4) %

In the current amendment, the firm complies with the DBE's request. However, the firm is also proposing new specifications for its test product which differ from the DBE's recommended specifications.

The firm's proposed specifications are as follows:

6 hr: (b) (4) %
24 hr: (b) (4) %
48 hr: (b) (4) %
72 hr: (b) (4) %

The firm provided additional dissolution testing data on an exhibit and packaging batch of its test product. After review of the dissolution testing and dissolution consultation (See Appendix, 8.2), the DBE agrees with the firm's proposed specifications. The DBE acknowledges the firm's submission of the additional dissolution data using the FDA-recommended method. Based on the data, the firm's proposed specifications for its test product are acceptable. However, the dissolution testing is still incomplete. The firm is requested to provide comparative dissolution testing in at least three additional dissolution media (i.e., pH 1.2, 4.5, and 6.8 buffer) to demonstrate the effect of potential dose dumping, if any[1, 2]. A multipoint dissolution profile should be obtained using a discriminating agitation speed. A surfactant may be used with the appropriate justification. The dissolution testing should be conducted until at least 80% of the labeled amount of drug is released.

The fasting BE Study (No. AA31201) is acceptable. However, the application is still **incomplete** pending the firm's submission of additional dissolution testing data for its test and reference products.

[1] Protocol Review: V:\firmsam (b) (4) \ltrs&rev\03063p1103.doc
[2] V:\firmsnz\Watson\ltrs&rev\76709a0104.doc

2 TABLE OF CONTENTS

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3 BACKGROUND

On 23 February, 2007, the firm submitted a single-dose, two-way crossover, *in vivo* BE study under fasting conditions comparing its test product, Scopolamine Transdermal System, 1 mg/72 hr, to the corresponding reference product, TransdermScop®, 1 mg/72 hr. The BE study results are provided in the table below[3].

Scopolamine, 1.31 mg/72 hr Fasting Bioequivalence Study No. AA31201, N=28 (Male=13 and Female=15) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (pg·hr/mL)	6377	7001	0.91	81.22 - 102.16
AUC∞ (pg·hr/mL)	6554	7139	0.92	82.52 – 102.15
Cmax (pg/mL)	128.44	121.85	1.05	92.03 - 120.74

The fasting BE study is acceptable.

The firm has conducted comparative dissolution testing on all strengths using the FDA-recommended dissolution method (DFS[4,5]). On 20 September, 2007, the firm submitted its response to DBE deficiency following dissolution review. The bioequivalence amendment consisted of the requested individual dissolution data of 12 units of the test and reference products using the FDA-recommended method. However, the specifications as proposed by the firm were found to be unacceptable based on the data submitted and therefore the DBE recommended different dissolution specifications. The firm's and DBE-recommended specifications are provided in the table below.

Time Point	Firm's proposed specification (20 September, 2007)	FDA-recommended specifications (30 October, 2007)	Firm's proposed specification (10 March, 2008)
6 hours		(b) (4)	
24 hours			
48 hours			
72 hours			

[3] Division of System Files v 2.0. ANDA 78-830. Bioequivalence Review N 078830 N 000 23-Feb-2007.
[4] Division of System Files v 2.0. ANDA 78-830. Bioequivalence Dissolution Review N 078830 N 000 20-Sep-2007.
[5] Division of System Files v 2.0. ANDA 78-830. Bioequivalence Dissolution Review N 078830 N 000 23-Feb-2007.

In a deficiency letter dated 30 November, 2007[6], the firm was asked to acknowledge the acceptance of the specifications as recommended by the DBE.

The application was deemed incomplete due to incomplete dissolution testing for the firm's test product.

A Division of Scientific Investigations (DSI) inspection[7] was conducted for the clinical end point study. The study was conducted by Novum Pharmaceutical Research Services. Following the evaluation of the inspectional findings[8], DSI concluded that data from the study was acceptable.

4 DEFICIENCY LETTER COMMENT

4.1 *Deficiency Comment No. 01*

1. *Your dissolution data as submitted using the following FDA-recommended dissolution method are acceptable:*

   The dissolution testing should be conducted in 25 x 150 mm test tubes containing 20 mL of distilled water at 32°C ± 0.3°C using USP apparatus 7 (reciprocating disk) at a stroke of 2-3 cm at a rate of 30-60 cycles/minute.

   However, based on the data submitted, your proposed dissolution specifications are not acceptable. Please acknowledge your acceptance of the following DBE-recommended dissolution specifications:

   6 hr: (b) (4) *%*

   24 hr: (b) (4) *%*

   48 hr: (b) (4) *%*

   72 hr: (b) (4) *%*

Firm's Response to Deficiency Comment No. 01

Perrigo acknowledges and accepts the DBE-recommended dissolution method and conditions as noted in the December 3, 2007, DBE deficiency letter, and confirms that this dissolution method will be utilized for release and stability testing of the Scopolamine Transdermal Therapeutic System, 1 mg/72 hr, Prescription Drug Product.

[6] Division of System Files v 2.0. ANDA 78-830. Bioequivalence Deficiency N 078830 N 000 23-Feb-2007.
[7] Division of System Files v 2.0. ANDA 78-830 OGD DSI Inspection Request N 078830 N 000 23-Feb-2007
[8] Division of System Files v 2.0. ANDA 78-830 Review of Clinical Inspection N 078830 N 000 23-Feb-2007

In reference to the DBE-recommended dissolution specifications, Perrigo respectfully proposes different ranges based on the following:

- Additional data has been generated for both the Exhibit batch, Lot # 35409, and for the alternate packaging batch, Lot # 35561, submitted January 4, 2008. Twenty-four patches from each of the two lots were tested for drug release to simulate the L1, L2 and L3 progression in accordance with USP chapter <724> for transdermal dosage forms. The data summarized below supports the proposed ranges.
- The stability data for the two batches summarized below has been compiled and evaluated in conjunction with the additional data.
- The original ranges submitted have been significantly tightened in consideration of the available data. Ranges that originally varied from 39% to 79% have all been reduced to a range of 25%.
- The new ranges will provide adequate control for the life of the product.

Batch	Time Points (results in %TDR)						
	1 hour	2 hours	4 hours	6 hours	24 hours	48 hours	72 hours
# 35409 (Average of 24 patches)	[redacted] (b) (4)						
# 35561 (Average of 24 patches)							
Stability Projects Average							
Overall Average	**46**	**49**	**53**	**55**	**74**	**97**	**110**

The comprehensive results are reported in the attached Scopolamine Drug Release Evaluation tables.

Based on the comprehensive test results reported herein for the Exhibit batch, Lot #35409, for the alternate packaging batch, Lot #35561, and the stability data for both batches, and in accordance with USP Chapter <724> for transdermal dosage forms, Perrigo suggests the following drug release specifications (in %TDR) to be used in place of the DBE-recommended dissolution specifications:

Time Points	Overall Average	Proposed Specification	FDA Specification	Original Perrigo Specifications
6 hours	55	[redacted] (b) (4)		
24 hours	74			
48 hours	97			
72 hours	110			

The ranges proposed for each of the time points are based on the "Overall Average" minus/plus 12.5 percentage points. The original ranges submitted have been significantly tightened in consideration of the available data. Ranges that originally varied from [redacted] (b) (4) % have all been reduced to a range of [redacted] (b) (4). However, as noted on page 2 of the

specifications, these ranges are based upon limited and will be re-evaluated after ten commercial lots.

5 REVIEWER'S COMMENT

Note: The firm's proposed dissolution specifications differ from the DBE-recommended specifications. The dissolution data of the packaging batch, exhibit batch and stability data have been considered by the reviewer and the dissolution consult expert in the acceptance of firm's proposed specifications.

1. The firm provided additional comparative dissolution testing data for an exhibit and packaging batch of its test product. The firm conducted dissolution testing on 24 dosage units each from exhibit batch and packaging batch. The firm's proposed specifications differ from the DBE (for details please refer to section 4.1). The DBE accepts the firms proposed specifications based on the data submitted. The ranges proposed for each of the time points were based on the "Overall Average" minus/plus 12.5 percentage points.

2. The firm's application is incomplete pending submission of comparative dissolution testing data in at least three additional dissolution media (i.e., pH 1.2, 4.5, and 6.8 buffer) for its test and reference products to demonstrate the effect of dose dumping, if any. The comparative *in vitro* dissolution testing conducted by Perrigo R & D Company on its Scopolamine Transdermal System, 1 mg/72 hr, Lot # 35409 (Exhibit batch) and Lot # 35561(Packaging batch) is ***incomplete***.

   The dissolution testing should be conducted using the FDA-recommended method of 25 x 150 mm test tubes containing 20 mL of distilled water at 32ºC ± 0.3ºC using USP Apparatus 7 (reciprocating disk) at a stroke of 2-3 cm at a rate of 30-60 cycles/minute. The test product should meet the following specifications:

   6 hr: (b) (4)%
   24 hr: (b) (4)%
   48 hr: (b) (4)%
   72 hr: (b) (4)%

   Note: The dissolution specifications are established based on the dissolution data on 12 dosage units of the fresh lots and not stored lots.

   The Division of Bioequivalence (DBE) acknowledges the firm's submission of the additional dissolution data using the FDA-recommended method. Based on the data, the firm's proposed specifications for its test product are acceptable. However, the dissolution testing is still incomplete pending submission of the requested additional dissolution data.

   Note: Additional dissolution testing data in at least three additional dissolution media (i.e., pH 1.2, 4.5 and 6.8 buffer) was requested for other ANDA's on transdermal

drug products (i.e., fentanyl[9]).The reason for the request is the pH of the skin may undergo changes and the dissolution testing at varying pHs may be used to possibly demonstrate the effect of dose dumping, if any.

6 DEFICIENCY COMMENT

The firm is requested to conduct and submit additional comparative *in vitro* dissolution testing in at least three different media (i.e., pH 1.2, 4.5, and 6.8 buffers) on 12 dosage units of the test and reference products. Agitation speed may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The firm is requested to conduct dissolution testing until at least 80% of the labeled amount of drug is released.

Note: If possible, the dissolution testing should be conducted on the same lots of the test and reference products used in its bioequivalence study.

7 RECOMMENDATIONS

The firm should submit additional dissolution testing on 12 dosage units of the test and reference products in at least three additional dissolution media (i.e., pH 1.2, 4.5, and 6.8 buffers). Agitation speed may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The firm is requested to conduct dissolution testing until at least 80% of the labeled amount of drug is released.

Note: If possible, the dissolution testing should be conducted on the same lots of the test and reference products used in your bioequivalence study.

[9] V:\firmsnz\Watson\ltrs&rev\76709a0104.doc

8 APPENDIX

8.1 Additional Attachments

Scopolamine Transdermal Therapeutic System, 1 mg/72 hour
Drug Release Evaluation, Lot 35409 (Exhibit Batch)

Proposed specifications

	L1			L2		L3	
	Range, as is			10% of range		20% of range	
Time	Min	Max	Ave	Min	Max	Min	Max
6 h		(b) (4)	55		(b) (4)		(b) (4)
24 h			74				
48 h			97				
72 h			110				

Raw data evaluation

Patch #	1 h	2 h	4 h	6 h	24 h	48 h	72 h
1							(b) (4)
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
22							
23							
24							

Level 1
Level 2
Level 3

Evaluation of first 6 patches (Level 1 criterion)							
Average	45	47	50	53	71	94	108
Min							(b) (4)
Max							
SD	0.8	0.9	1.0	1.2	3.6	5.3	4.9
Evaluation of first 12 patches (Level 2 criteria)							
Average	46	48	51	54	73	97	109
Min							(b) (4)
Max							
SD	1.1	1.3	1.7	2.1	4.7	7.0	6.1
Evaluation of all 24 patches (Level 3 criteria)							
Average	48	48	52	54	72	94	107
Min							(b) (4)
Max							
SD	1.1	1.4	1.9	2.1	4.4	7.3	7.1

Scopolamine Transdermal Therapeutic System, 1 mg/72 hour
Drug Release Evaluation, Lot 35561 (Alternate Packaging Batch)

Proposed specifications

	L1			L2		L3	
	Range, as is			10% of range		20% of range	
Time	Min	Max	Ave	Min	Max	Min	Max
6 h	(b) (4)		55	(b) (4)		(b) (4)	
24 h			74				
48 h			97				
72 h			110				

Raw data evaluation

Patch #	1 h	2 h	4 h	6 h	24 h	48 h	72 h
1							(b) (4)
2							
3							
4							
5							
6							
7							
8							
9							
10							
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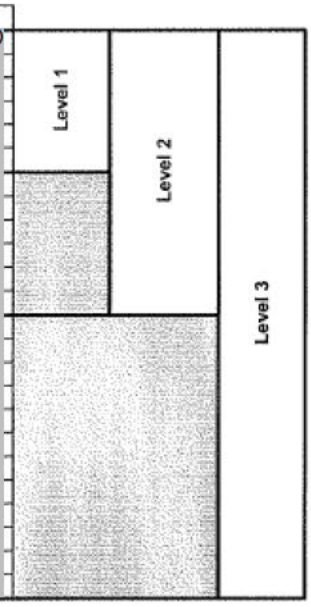

Evaluation of first 6 patches (Level 1 criterion)							
Average	47	51	55	58	76	97	111
Min							(b) (4)
Max							
SD	2.9	3.1	3.4	3.4	4.5	9.2	6.1
Evaluation of first 12 patches (Level 2 criteria)							
Average	47	51	56	58	77	98	112
Min							(b) (4)
Max							
SD	2.7	2.8	3.3	3.3	4.8	8.4	6.6
Evaluation of all 24 patches (Level 3 criteria)							
Average	48	52	56	59	77	100	113
Min							(b) (4)
Max							
SD	2.6	2.7	3.1	3.0	4.8	9.5	7.7

Note: These tables were provided by the firm.

8.2 Dissolution Consult

From: Jiang, Xiaojian
Sent: Sunday, May 18, 2008 4:13 PM
To: Mandula, Haritha
Subject: FW: For Scopolamin TDS

Hi, Haritha:
I forgot to mention in last e-mail that I did not find multimedia dissolution data for this product. Based on my knowledge, the
TDS is considered as ER product. The control document for this product did not mention the multimedia testing. I can see that may be because there is no biowaiver request, a BE study may assure no dose dumping for this product in vivo. Please consult April and Hoai if the multimedia testing is necessary.

Thanks

Xiaojian Jiang, Ph.D.
Division of Bioequivalence, OGD, CDER, FDA
E-mail: xiaojian.jiang@fda.hhs.gov
1356 MPNI, Phone: 240-276-8799

From: Jiang, Xiaojian
Sent: Sunday, May 18, 2008 3:24 PM
To: Mandula, Haritha
Cc: Braddy, April; Jiang, Xiaojian
Subject: RE: For Scopolamin TDS

Hi, Haritha:

I am sorry to response you late. I agree with your opinion that based on the current submitted data, the firm's proposed specifications are reasonable. In your review, you might want to include information for the alternative packaging batch,lot# 35561 since this is not a biobatch. I found the information in CMC review#2 (DFS). This batch was submitted in Jan. 2008 to support an alternative packaging configuration.

I think that a specification at 12 hrs is not necessary because of the following reasons:

1) based on the test formulation (the test formulation is similar to the RLD having two drug adhesive layers separated by a rate controlling membrane)) and the labeling (of the RLD), the initial phase of release is actually a "immediate release or a priming" of the dose due to drug release from the first layer of adhesive matrix. The data show a (b)(4)% release at 1 hrs and slightly increase to (b)(4)% at 6 hrs. Afterwards, the release rate is decreased. A specification at 6 hrs sufficiently controls this initial fast release phase. Specifications at 24, 48, and 72 control the more ER release phase of this product.
2) As per guidance, the specifications should cover the early, middle and late stages of the dissolution profile. The current specifications met this requirement.

For your information, the firm's specification is based on the total delivered dose which if 1 mg. Therefore, the percentage release can exceed 110% because the TDS contains 1.3 mg drug.

I hope you can find this information helpful for your final decision.

Thanks

Xiaojian Jiang, Ph.D.
Division of Bioequivalence, OGD, CDER, FDA
E-mail: xiaojian.jiang@fda.hhs.gov
1356 MPNI, Phone: 240-276-8799

From: Mandula, Haritha
Sent: Friday, May 16, 2008 9:28 AM
To: Jiang, Xiaojian
Subject: RE: For Scopolamin TDS

Hi Xiaojian,

The NDA states percent of label claim (1.5 mg) of scopolamine released with time. I agree with the firms proposed specifications. (b) (4) My only concern is that, the specifications as proposed by the DBE and even by the firm are much different when compared with the NDA Also NDA had a 12 hour sampling time point and specification too for 12 hr (because this is a biphasic release and initial phase is 0-12 hr).
Should we also request for a 12 hour sample time point with a specification?

From Bio study, median tmax is slightly different test vs ref (20 vs 18).
Cmax is not very different, higher in test than reference (RMSE variability associated with Cmax is 0.2978, CI: 92.03-120.74).

I am further looking into their formulation, if this can be explained by differences in formulations.

The adverse effect profile from bio study does not raise any concerns either.

Thank you for your time and your advice in this regard,

Sincerely,
Haritha.

From: Jiang, Xiaojian
Sent: Thursday, May 15, 2008 9:39 PM
To: Mandula, Haritha
Subject: For Scopolamin TDS

Hi, Haritha:
Is that possible you can provide me your proposal for the firm's request?

I did not get chance to take a look at your data today. I will take a look the first thing tomorrow.

Thanks

Xiaojian Jiang, Ph.D.
Division of Bioequivalence, OGD, CDER, FDA
E-mail: xiaojian.jiang@fda.hhs.gov
1356 MPNI, Phone: 240-276-8799

BIOEQUIVALENCE DEFICIENCY

ANDA: 78-830

APPLICANT: Perrigo Pharmaceuticals

DRUG PRODUCT: Scopolamine Transdermal System, 1 mg/72 hr

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

We acknowledge that you have submitted additional dissolution data using the FDA-recommended dissolution method. However, your dissolution testing is still **incomplete**. Please submit comparative *in vitro* dissolution testing on 12 dosage units of the test and reference products in at least three different pH media (i.e., pH 1.2, 4.5 and 6.8 buffers). Agitation speed may have to be increased if appropriate. It is acceptable to add a small of surfactant, if necessary. Please conduct dissolution testing until at least 80% of the labeled amount of the drug is released. Also, if possible, the dissolution testing should be conducted on your biostudy lots of the test and reference products.

Please submit the comparative dissolution results which should include the individual dosage unit data as well as the mean, range, %CV at each time point for the 12 dosage units tested, and dates of dissolution testing. In addition, please submit the dissolution testing data summary table (Table 5) with the above data. More information on the electronic Common Technical Document (eCTD) format for BE summary tables are provided on http://www. fda.gov/cder/ogd/DBE_tables.pdf.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

8.3 Outcome Page

ANDA: 78-830

Completed Assignment for 78830 ID: 5602

Reviewer: Mandula, Haritha **Date Completed:**
Verifier: Braddy, April **Date Verified:**
Division: Division of Bioequivalence
Description: Study Amendment

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
5602	3/10/2008	Other	Study Amendment	1	1
				Bean Total:	1

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/s/

Haritha Mandula
6/23/2008 04:25:43 PM
BIOPHARMACEUTICS

April Braddy
6/23/2008 04:26:29 PM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
6/24/2008 08:32:14 AM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78830		
Drug Product Name	Scopolamine Transdermal System		
Strength(s)	1 mg/72 hr		
Applicant Name	Perrigo R&D Company		
Address	515 Eastern Ave. Allegan, MI 49010		
Applicant's Point of Contact	Diane L. Morgan		
Contact's Telephone Number	269-686-1729		
Contact's Fax Number	269-673-7655		
Original Submission Date(s)	February 23, 2007		
Submission Date(s) of Amendment(s) Under Review	September 20, 2007 (Bioequivalence amendment)		
Reviewer	Haritha Mandula		
Study Number (s)	AA31201		
Study Type (s)	Bioequivalence		
Strength (s)	1 mg/72 hr		
Clinical Site	MDS Pharma Services		
Clinical Site Address	2350 Cohen Street, Saint-Laurent, Montreal, Quebec, H4R 2N6, Canada		
Analytical Site	(b) (4)		
Analytical Site Address			
OUTCOME DECISION	**INCOMPLETE**		

1 EXECUTIVE SUMMARY

This is the FIRST GENERIC application for this drug product. This application contains the results of a fasting bioequivalence (BE) study comparing the test product, Scopolamine Transdermal System, 1 mg/72 hr, to the corresponding reference product, TransdermScop®, 1 mg/ 72 hr. The BE study was designed as a single site, open label, randomized, single dose, two-way crossover study in healthy male and female subjects. The firm's fasting study is acceptable. The results are summarized in the table below.

Scopolamine, 1.31 mg/72 hr Fasting Bioequivalence Study No. AA31201, N=28 (Male=13 and Female=15) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (pg·hr/mL)	6377	7001	0.91	81.22 - 102.16
AUC∞ (pg·hr/mL)	6554	7139	0.92	82.52 – 102.15
Cmax (pg/mL)	128.44	121.85	1.05	92.03 - 120.74

The firm has conducted acceptable comparative dissolution testing on all strengths using the FDA-recommended dissolution method (DFS). However, the specifications as proposed by the firm were found to be unacceptable based on the data submitted and DBE has recommended different dissolution specifications. The firm is asked to acknowledge the acceptance of the specifications as recommended by the DBE.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is incomplete pending the firm's acknowledgement of the FDA-recommended dissolution specifications.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Scopolamine Transdermal System, 1 mg/72 hr
Reference Product	TransdermScop®, 1 mg/72 hr
RLD Manufacturer	Alza Corporation (Distributed by Novartis Consumer Health, Inc.)
NDA No.	017874
RLD Approval Date	December 31, 1979
Indication	The drug product is used for the prevention of nausea and vomiting associated with motion sickness and recovery from anesthesia and surgery.

3.2 PK/PD Information

Bioavailability	Scopolamine is well-absorbed percutaneously. Following application to the skin behind the ear, circulating plasma levels are detected within 4 hours with peak levels being obtained, on average, within 24 hours[1].
Food Effect	N/A
Tmax	Peak levels are obtained within 24 hours[1].
Metabolism	Scopolamine is extensively metabolized and conjugated with less than 5% of the total dose appearing unchanged in the urine. The metabolites have not been characterized.
Excretion	The exact elimination pattern of scopolamine has not been determined. Following patch removal, plasma levels decline in a log linear fashion. Less than 10% of the total dose is excreted in the urine as parent and metabolites over 108 hours[2].
Half-life	Observed half-life is approximately 9.5 hours[1].
Drug Specific Issues (if any)	Scopolamine should not be used in case of an allergic reaction or in case of existing narrow angle glaucoma. The patch should not be used in children and should be used with caution in the elderly.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	1, fasting

1.	**Type of study:**	Fasting
	Design:	Single site, open label, randomized, single dose, two-way crossover study
	Strength:	1 mg/72 hr
	Subjects:	Normal healthy males and females subjects

[1] PDR® Electronic Library ™
[2] PDR® Electronic Library ™

	Additional Comments:	

Analytes to measure (in plasma/serum/blood):	Scopolamine
Bioequivalence based on:	Scopolamine (90% CI)
Waiver request of in-vivo testing:	None
Source of most recent recommendations:	OGD Control # 02-557, 9/27/2002, (b) (4) (b) (4) OGD Control #03-093, 2/11/2003, (b) (4) (b) (4) OGD Control # 05-0492, 5/2/2005, Perrigo OGD Control # 05-0796, 6/27/2005, (b) (4) OGD Control # 06-0355, 3/17/2006, (b) (4) OGD Control # 06-0332, 3/9/2006, (b) (4) Protocol # 96-016, 4/10/1996, (b) (4) Protocol # 98-006, 02/12/1998 (b) (4) Protocol # 02-059, 11/14/2002, amendment 01/30/2003, (b) (4) Protocol # 04-037, 7/26/2004, (b) (4) Protocol # 06-085, 8/8/2006, (b) (4) Protocol # 06-070, 3/10/2006, (b) (4)
Summary of OGD or DBE History (for details, see Appendix 4.4):	A firm seeking marketing approval of a generic version of scopolamine transdermal therapeutic system should do the following: (1) conduct a single-dose fasting in vivo bioequivalence study; (2) evaluate skin irritation and sensitization; (3) evaluate product adherence; and (4) characterize in vitro release. Because of safety concerns regarding continuous duration of therapy for 21 days or longer, the skin irritation and sensitization studies should be conducted with a placebo patch. The placebo patch should be identical to the proposed generic product except for the absence of scopolamine. Requests about manufacturing site are deferred to the Division of Chemistry[3].

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	Yes	1
Waiver requests	No	
BCS Waivers	No	

[3] OGD Control # 02-557 (submission date 9/27/02)

Clinical Endpoints	Yes	
Failed Studies	No	
Amendments	Yes	2

3.5 Pre-Study Bioanalytical Method Validation

Validation Summary	(b) (4)
Analyte	Scopolamine
Internal Standard (IS)	d_3-scopolamine
Method Description	Liquid-liquid extraction with analysis/detection by LC-MS/MS
Limit of Quantitation (pg/mL)	5.00 pg/mL
Recovery of Drug (%)	86% at 20.0 pg/mL 91% at 100 pg/mL 92% at 375 pg/mL.
Average Recovery of IS (%)	92%
Standard Curve Concentrations (pg/mL)	5.00, 10.0, 20.0, 40.0, 60.0, 100, 200, 400 and 500 pg/mL
QC Concentrations (pg/mL)	5.00, 15.0, 50.0, 150 and 375 pg/mL
QC Intraday Precision Range (%CV)	2.1% to 5.9%
QC Intraday Accuracy Range (%Bias)	-10.6% to 4.0%
QC Interday Precision Range (%CV)	3.9% to 7.2%
QC Interday Accuracy Range (%Bias)	-4.2% to -0.8%
Bench-top Stability (hrs)	26 hours in polypropylene tubes at ambient temperature under UV-shielded light
Stock Stability (days)	100 days at approximately 1000 µg/mL in 50:50 methanol:water in a polypropylene container at 5°C
Processed Stability (hrs)	Processed Sample Integrity: 124 hours in amber injection vials with polypropylene inserts at 5°C Post-Preparative Stability: 149 hours in amber injection vials with polypropylene inserts at 5°C
Freeze-Thaw Stability (Cycles)	6 cycles in polypropylene tubes at -20°C under UV-shielded light
Long-Term Storage Stability (days)	292 days in polypropylene tubes at -20°C
Dilution Integrity	up to 2500 pg/mL
Selectivity	No significant matrix effect was observed in any of the 10 human plasma (EDTA) lots that were unspiked (i.e., blanks), spiked at the concentration of the LLOQ (5.00 pg/mL) and at the concentration of the high QC (375 pg/mL) sample.

SOPs submitted	(b) (4) Chromatographic and Spectrometric Methods: Validation	Effective Date: (b) (4) (b) (4)
Bioanalytical method is acceptable	Acceptable	

Comments on the Pre-Study Method Validation:

Acceptable

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 No.(M/F) Type Age: Mean (Range)	Mean Parameters (± SD)					
					C_{max} (pg/mL)	T_{max} (h)	AUC_{0-t} (pg·h/mL)	AUC_{∞} (pg·h/mL)	$T_{½}$ (h)	K_{el} (1/h)
AA31201	A RANDOMIZED, TWO-WAY CROSSOVER STUDY TO EVALUATE THE BIOEQUIVALENCE, TOLERABILITY AND ADHESION OF AN INVESTIGATIONAL TRANSDERMAL SCOPOLAMINE SYSTEM VERSUS TRANSDERM SCOP® IN HEALTHY MALE AND FEMALE SUBJECTS	Randomized Single-dose Crossover	Test Product: A: Aveva DDS, Inc. 1 x 1 mg/72hours scopolamine system, transdermal; Lot No.: 35409	28 healthy adult volunteers (13M/15F) completed the study. Mean age based on the 28 subjects who completed the study (13M/15F): 40.6 years (24-55 years)	142.854 ± 61.8914	20.00 (6.00-74.00)	6812.6 ± 2158.03	6972.5 ± 2139.27	14.318 ± 4.4156	0.05244 ± 0.014372
			Reference Product: B: ALZA Corporation 1 x 1 mg/72hours TransdermScop®, transdermal Lot No.: 0526942*		130.554 ± 53.9259	18.00 (4.00-80.00)	7275.9 ± 1880.26	7438.9 ± 1890.47	14.331 ± 2.9926	0.05054 ± 0.014372

* bulk product Lot #20711701 as per Certificate of Conformance

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Scopolamine Dose 1mg/72 hr Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study AA31201					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg hr/mL)	6377	7001	0.91	81.22	102.16
AUC∞ (pg.hr/mL)	6554	7139	0.92	82.52	102.15
Cmax (pg/mL)	128.44	121.85	1.05	92.03	120.74

For Subject No. (b) (6) the time of the blood draw at the 48-hour time point in Period 1 is questionable. Hence an additional analysis was performed setting the concentration at this time point to missing. Reanalysis of the data set did not result in any change in the outcome of the study. The results are presented in the table below.

Scopolamine Dose 1mg/72 hr Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study AA31201					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg hr/mL)	6375	7001	0.91	81.19	102.11
AUC∞ (pg.hr/mL)	6551	7139	0.92	82.49	102.10
Cmax (pg/mL)	128.31	121.85	1.05	91.96	120.58

Table 3. Reanalysis of Study Samples

Study No. AA31201								
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	0	0.00	0.00	0	0	0.00	0.00
UISR - Unacceptable Internal Standard Response	1	4	0.07	0.30	1	4	0.07	0.30
Total	1	4	0.07	0.30	1	4	0.07	0.30

Total number of samples analyzed = 1344

Did use of recalculated plasma concentration data change study outcome?

No

Comments from the Reviewer:

Reassays were performed due to unacceptable Internal Standard Response. The SOP [redacted](b) (4) "Reporting of data generated from the analysis of biological matrices and the reassay of samples" provided the criteria for identifying samples with variable IS response.

Summary of Adhesion Studies:

Ninety percent of the subjects or more obtained adherence scores of 0 (90% adhered) or 1 (75% to less than 90% adhered) following treatment with the Aveva patch and TransdermScop®, regardless of time points. The ratio of Least Squares Mean of the Aveva patch over TransdermScop® for the % adhesion was 97% with a lower 95% confidence interval limit of 91%. Adhesion of the patches at the application site was comparable between the two products and demonstrated non-inferiority of the Aveva patch. Subject No. [redacted](b) (6)(treatment B) was withdrawn from the study per Sponsor's request due to detachment (adhesion code 4: patch detached or patch completely off the skin) of patch on Day 2 of period 2. This subject was excluded

from the statistical analysis. Subjects reporting adhesion code 2 (50% to <75% adhered or less than half of the system lifting off the skin) and 3 (<50% adhered but not detached or more than half the system lifting off of the skin but not detached) were less than 11% at all the time points. No auxiliary tape or other substance was applied to the patch to maintain adhesion.

Table 14.3.5. Patch Adhesion Assessment - Frequency Counts by Treatment and Time Point

Hour	Adhesion Code	Treatment A	Treatment B
11.83	0	22 (75.9%)	25 (83.3%)
	1	6 (20.7%)	5 (16.7%)
	3	1 (3.4%)	
23.83	0	12 (41.4%)	14 (46.7%)
	1	15 (51.7%)	16 (53.3%)
	2	2 (6.9%)	
35.83	0	24 (82.8%)	24 (80.0%)
	1	2 (6.9%)	5 (16.7%)
	2	3 (10.3%)	
	4		1 (3.3%)
47.83	0	18 (62.1%)	12 (40.0%)
	1	9 (31.0%)	15 (50.0%)
	2	2 (6.9%)	2 (6.7%)
	4		1 (3.3%)
59.83	0	24 (82.8%)	24 (82.8%)
	1	4 (13.8%)	4 (13.8%)
	2		1 (3.4%)
	3	1 (3.4%)	
71.83	0	7 (24.1%)	9 (31.0%)
	1	19 (65.5%)	18 (62.1%)
	2	2 (6.9%)	2 (6.9%)
	3	1 (3.4%)	

Note: 0= 90% adhered (essentially no lift off of the skin)
1= 75% to less than 90% adhered (some edges only lifting off of the skin)
2= 50% to less than 75% adhered (less than half of the system lifting off of the skin)
3= Less than 50% adhered but not detached (more than half the system lifting off of the skin)
4= Patch detached (patch completely off the skin)

Treatment A = Scopolamine (Aveva DDS Lot #35409; exp:01/07) 1 x 1.31 mg, fasted (test product)
Treatment B = Transderm-Scop(R) (Alza Corp, Palo Alto, CA; Lot #0526942; exp: 08/2008) 1 x 1.5 mg, fasted (reference product)

Summary of Irritation Studies:

Irritation results from the application site evaluation performed 30 minutes and 24 hours after patch removal were similar for both treatments, with more than 79% of the subjects presenting no evidence of irritation 24 hours after patch removal. The

most frequently occurring adverse event was application site erythema, observed in 80% of subjects (58.6% Aveva, 70.0% TransdermScop®). Other events occurring in 10% of subjects or more were headache, blurred vision, dry mouth, nausea, application site reaction (glazed appearance), dry throat, dizziness, vomiting, mydriasis, and vessel puncture site bruise.

3.7 Formulation

Location in appendix	Section 4.2, Page 33
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?	

Comments:

All the ingredients were found to be within IIG limits which have also been confirmed by chemistry review. (b) (4)

(b) (4)

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DFS
Source of Method (USP, FDA or Firm)	FDA
Medium	Distilled Water
Volume (mL)	20 mL
USP Apparatus type	7 (reciprocating disk)
Rotation (rpm)	Stroke of 2-3 cm at a rate of 30-60 cycles/minute
DBE-recommended specifications	6 hr: (b) (4) %, 24 hr: (b) (4) %, 48 hr: (b) (4) %, 72 hr: (b) (4) %
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?	**Pending the firm's acknowledgement of the FDA-recommended specifications.**
If not then why?	

F2 metric, biostudy strengths compared to other strength(s)		
Biostudy Strength	**Other Strength**	**F2 metric for test when compared to RLD**
1.31 mg/72 hr	-	53.34

Comments:

(b) (4)

On September 10, 2007, DBE (Reviewer: Svetlana Cherstniakova) completed review of the dissolution testing portion of the original ANDA submission dated February 23, 2007. The dissolution testing was incomplete and the firm was asked to provide dissolution data including individual data of drug release for the test and reference products for 12 units (Letter date: September 13, 2007). The firm submitted the amendment on 20 September, 2007. The dissolution review was completed on 10/30/2007. The review has accepted the dissolution results. However, the specifications as proposed by the firm were found to be unacceptable based on the data submitted and DBE has recommended different dissolution specifications. The firm was asked to acknowledge the acceptance of the specifications as recommended by DBE. Since the dissolution amendment review above was completed at approximately the same time as the current bioequivalence study review, the letter requesting the firm's acknowledgement of the proposed specifications will also be included in the current review and will be sent at the completion of the current bioequivalence review (instead of following the dissolution amendment review).

3.9 Deficiency Comments

Per the dissolution amendment review (completed October 30, 2007, in DFS), the firm has conducted dissolution testing for the test and RLD products using the FDA-recommended dissolution method. The firm has proposed its own specifications for the test product. However, the firm's proposed specifications were found unacceptable by the dissolution reviewer. The DBE has recommended different specifications based on the data submitted (See under section 3.8 In Vitro Dissolution above). The firm is asked to acknowledge the FDA-recommended dissolution method and specifications. The dissolution testing is considered incomplete at this time.

3.10 Recommendations

1) The Division of Bioequivalence accepts the fasting BE study No.AA31201 conducted by the Perrigo Pharmaceuticals on its Scopolamine Transdermal System, 1 mg/72 hr, lot # 35409 comparing it to ALZA Corporation's TransdermScop®, 1 mg/72 hr, lot # 0526942.

2) The firm's in vitro dissolution testing is incomplete pending its acceptance and acknowledgment of the FDA method and specifications. The dissolution testing should be conducted in 25 x 150 mm test tubes containing 20 mL of distilled water at 32ºC ± 0.3ºC using USP apparatus 7 (reciprocating disk) at a stroke of 2-3 cm at a rate of 30-60 cycles/minute. The test product should meet the following specification(s):

   6 hr: (b) (4)%
   24 hr: (b) (4)%
   48 hr: (b) (4)%
   72 hr: (b) (4)%

3.11 Comments for Other OGD Disciplines

Discipline	Comment

APPEARS THIS WAY ON ORIGINAL

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	AA31201
Study Title	A RANDOMIZED, TWO-WAY CROSSOVER STUDY TO EVALUATE THE BIOEQUIVALENCE, TOLERABILITY AND ADHESION OF AN INVESTIGATIONAL TRANSDERMAL SCOPOLAMINE SYSTEM VERSUS TRANSDERMSCOP® IN HEALTHY MALE AND FEMALE SUBJECTS
Clinical Site (Name, Address, Phone #)	MDS Pharma Services 2350 Cohen Street Saint-Laurent, Montreal Quebec, H4R 2N6 Canada Tel.: (514) 333-0042
Principal Investigator	Gaetano Morelli, M.D. Director Global Medical Affairs, Early Clinical Research
Dosing Dates	Period 1 dosing: 18/Sep/2006; Period 2 dosing: 25/Sep/2006
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	From 10-Oct-2006 to 26-Oct-2006
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)	Study samples were stored from sample collection to the end of sample analysis at a nominal temperature of -20° C for a duration not exceeding 39 days.

Table 5. Product information

Product	Test	Reference
Treatment ID	A	B
Product Name	Scopolamine Transdermal System	Transderm Scop®
Manufacturer	Aveva DDS	ALZA Corporation
Batch/Lot No.	35409	0526942 (bulk lot # 20711701)
Manufacture Date	07/26/06	N/A
Expiration Date	N/A	08/08
Dose (Strength)	1 mg/72 hr	1 gm/72 hr
Drug Content (Load)	1.31 mg*	1.5 mg*
Dosage Form	Film, Extended Release	Film, Extended Release
Bio-batch Size	(b) (4)	N/A
Production Batch Size		N/A
Content Uniformity (mean, %CV)	100.4 (0.8% RSD)	N/A
Dose Administered	One patch	One patch
Route of Administration	Transdermal	Transdermal

* As this is a transdermal product, the amount of drug substance delivered over time is termed the dose (or strength), while the actual amount of the drug substance in the product is the drug content (or load). Although the drug content of scopolamine is different between the products (1.5 mg in the RLD vs. 1.3 mg in the Perrigo product), the amount delivered (strength) is the same in both products (1 mg/72 hours).

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	30 Healthy adult subjects (15 males and 15 females) were enrolled and 28 subjects (13 males and 15 females) completed the study.
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB: 01, 03, 04, 07, 08, 11, 13, 14, 15, 18, 21, 22, 23, 26, 28 BA: 02, 05, 06, 09, 10, 12, 16, 17, 19, 20, 24, 25, 27, 29, 30
Blood Sampling Times	Pre-dose, 2, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 48, 60 72 (prior to patch removal) 74, 76, 78, 80, 82, 84, 96, 108 and 120 hours after patch application.
Blood Volume Collected/Sample	Blood samples (1 x 7 mL) were collected in blood collection tubes containing K3EDTA. A total of 48 blood samples (336 mL) were drawn during the study for the analysis of scopolamine in plasma for each subject who completed the study.
Blood Sample Processing/Storage	Plasma was obtained according to instructions provided by the analytical laboratory. Study samples were stored from sample collection at MDS PS to the end of sample analysis at a nominal temperature of -20°C for a duration not exceeding 39 days. An aliquot of human plasma (EDTA) containing the analyte and internal standard was extracted using a liquid-liquid extraction procedure.

IRB Approval	The protocol was reviewed and approved prior to study initiation on 25th July, 2006 by an Institutional Review Board convening at MDS Pharma Services in Montreal Quebec, Canada.
Informed Consent	Informed consent forms were approved by the Institutional Review Board on 25th, 26th and 28th July, 2006.
Length of Fasting	Food was restricted 10 hours predose until 4 hours postdose.
Length of Confinement	In each period, subjects were housed from approximately 12 hours before dosing until after the 120-hour post-dose events.
Safety Monitoring	Sitting vital signs (blood pressure and heart rate) were assessed each morning immediately prior to patch application, every 12hours throughout the confinement period, and at other times, if deemed necessary. When blood sampling and vital sign determinations occurred at the same time, the vital sign determinations were taken first. Vital signs were taken within approximately 30 minutes of the scheduled time. Subjects were instructed to inform the study physician and/or nurses of any adverse events that occurred during the study. Patch adhesion was evaluated within 10 minutes of each vital sign determination and within 10 minutes prior to patch removal during the wear period. Application site evaluation was performed at approximately 30 ± 5 minutes and 24 ±1 hour after the patch was removed. Subjects were instructed to inform the study physician and/or nurse of any adverse events (AEs) that occurred during the study. In addition, all hematology, serum chemistry, and urinalysis tests were repeated upon completion of the study. A physical examination and vital signs were also assessed on the final study day or early termination visit.

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

	Treatment Groups	
	Test Product N=28	Reference Product N=28
Age (Years)		
Mean±SD	40.6 ± 8.4	40.6 ± 8.4
Range	24 - 55	24 - 55
Age Groups (Years)		
18-39	14 (50%)	14 (50%)
40-64	14 (50%)	14 (50%)
Sex		
Female	15 (53.6%)	15 (53.6%)
Male	13 (46.4%)	13 (46.4%)
Race		
Black	1 (3.6%)	1 (3.6%)
Caucasian	27 (96.4%)	27 (96.4%)

	Treatment Groups	
	Test Product N=28	Reference Product N=28
Weight (kg)		
Mean±SD	72.3 ± 8.8	72.3 ± 8.8
Range	56.4 - 90.0	56.4 - 90.0
Height (cm)		
Mean±SD	167.3 ± 9.0	167.3 ± 9.0
Range	154 - 187	154 - 187
B.M.I (kg/m2)		
Mean±SD	25.8 ± 1.8	25.8 ± 1.8
Range	23.0 - 29.9	23.0 - 29.9

Table 8. Dropout Information, Fasting Bioequivalence Study

Study No. AA31201				
Subject No	**Reason for dropout/replacement***	**Period**	**Replaced?**	**Replaced with**
(b) (6)	Subject was withdrawn from the study as requested by the Sponsor due to detachment of the Alza (TransdermScop®) system, exact time is unknown	2nd Day of Period 2	NO	N/A
	Subject was withdrawn by the Investigator due to adverse events following the application of the Alza (TransdermScop®) system	After completion of Period 1	NO	N/A

Table 9. Study Adverse Events, Fasting Bioequivalence Study

Adverse Event (Classified according to MedDRA Version 9.0) System Organ Class Preferred Term	Test		Reference		Total	
Number of Subjects Dosed	29	(100%)	30	(100%)	30	(100%)
Number of Subjects With Adverse Events	22	(75.9%)	25	(83.3%)	27	(90%)
Number of Subjects Without Adverse Events	7	(24.1%)	5	(16.7%)	3	(10%)
Skin and subcutaneous tissue disorders	17	(58.6%)	21	(70%)	24	(80%)
Application site erythema	17	(58.6%)	21	(70%)	24	(80%)
Pruritus	0	(0%)	2	(6.7%)	2	(6.7%)
Erythema	0	(0%)	1	(3.3%)	1	(3.3%)
Rash generalised	0	(0%)	1	(3.3%)	1	(3.3%)

Adverse Event (Classified according to MedDRA Version 9.0) System Organ Class Preferred Term	Test		Reference		Total	
Nervous system disorders	7	(24.1%)	7	(23.3%)	13	(43.3%)
Headache	5	(17.2%)	7	(23.3%)	11	(36.7%)
Dizziness	2	(6.9%)	2	(6.7%)	4	(13.3%)
Post procedural dizziness	1	(3.4%)	0	(0%)	1	(3.3%)
Gastrointestinal disorders	6	(20.7%)	8	(26.7%)	11	(36.7%)
Dry mouth	3	(10.3%)	3	(10%)	6	(20%)
Nausea	3	(10.3%)	4	(13.3%)	5	(16.7%)
Vomiting	0	(0%)	3	(10%)	3	(10%)
Abdominal pain	0	(0%)	1	(3.3%)	1	(3.3%)
Bowel movement irregularity	0	(0%)	1	(3.3%)	1	(3.3%)
Constipation	0	(0%)	1	(3.3%)	1	(3.3%)
Flatulence	0	(0%)	1	(3.3%)	1	(3.3%)
Stomach discomfort	0	(0%)	1	(3.3%)	1	(3.3%)

Adverse Event (Classified according to MedDRA Version 9.0) System Organ Class Preferred Term	Test		Reference		Total	
Eye disorders	5	(17.2%)	5	(16.7%)	8	(26.7%)
Vision blurred	5	(17.2%)	5	(16.7%)	8	(26.7%)
Mydriasis	3	(10.3%)	0	(0%)	3	(10%)
Ocular hyperaemia	0	(0%)	2	(6.7%)	2	(6.7%)
Eye irritation	0	(0%)	1	(3.3%)	1	(3.3%)
Eye pruritus	0	(0%)	1	(3.3%)	1	(3.3%)
Eye swelling	0	(0%)	1	(3.3%)	1	(3.3%)
Respiratory, thoracic and mediastinal disorders	4	(13.8%)	3	(10%)	6	(20%)
Dry throat	3	(10.3%)	2	(6.7%)	5	(16.7%)
Cough	1	(3.4%)	1	(3.3%)	2	(6.7%)
Pharyngolaryngeal pain	1	(3.4%)	0	(0%)	1	(3.3%)
Rhinorrhoea	0	(0%)	1	(3.3%)	1	(3.3%)

Adverse Event (Classified according to MedDRA Version 9.0) System Organ Class Preferred Term	Test		Reference		Total	
General disorders and administration site conditions	5	(17.2%)	1	(3.3%)	6	(20%)
Application site reaction	4	(13.8%)	1	(3.3%)	5	(16.7%)
Feeling cold	1	(3.4%)	0	(0%)	1	(3.3%)
Feeling hot	1	(3.4%)	0	(0%)	1	(3.3%)
Puncture site pain	1	(3.4%)	0	(0%)	1	(3.3%)
Pyrexia	1	(3.4%)	0	(0%)	1	(3.3%)
Injury, poisoning and procedural complications	3	(10.3%)	1	(3.3%)	3	(10%)
Vessel puncture site bruise	3	(10.3%)	0	(0%)	3	(10%)
Scratch	0	(0%)	1	(3.3%)	1	(3.3%)
Psychiatric disorders	0	(0%)	2	(6.7%)	2	(6.7%)
Somnolence	0	(0%)	2	(6.7%)	2	(6.7%)
Musculoskeletal and connective tissue disorders	1	(3.4%)	1	(3.3%)	2	(6.7%)
Neck pain	1	(3.4%)	0	(0%)	1	(3.3%)
Pain in extremity	0	(0%)	1	(3.3%)	1	(3.3%)
Renal and urinary disorders	0	(0%)	1	(3.3%)	1	(3.3%)
Urinary tract infection	0	(0%)	1	(3.3%)	1	(3.3%)

Table 10. Protocol Deviations, Fasting Bioequivalence Study

Study No. AA31201			
Type	Subject #s (Screening)	Subject #s (Test)	Subject #s (Ref.)
At screening, the hematology tests for monocytes were > 5% of the allowed range for abnormal values*		(b) (6)	
At screening, the urinalysis tests for ketone level was > 5% of the allowed range for abnormal values*			
At screening, the urinalysis tests for blood was > 5% of the allowed range for abnormal values*			
Consumption of prune juice during study			

*There was no impact on subjects' safety as per the Principal Investigator. The subjects were placed on the study.

Comments on Dropouts/Adverse Events/Protocol Deviations:

Blood draw time deviations were not significant and accounted for < 2% deviation. For Subject No (b) (6) the time of the blood draw at the 48-hour time point in period 1 was

reported to be questionable. It was reported that the blood sample collection time may be incorrect by a few minutes. Reanalysis by the reviewer setting the concentration of this sample to missing did not change the study outcome.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. AA31201 Analyte Name Scopolamine									
Parameter	**Standard Curve Samples**								
Concentration (pg/mL)	5.00	10.0	20.0	40.0	60.0	100	200	400	500
Inter day Precision (%CV)	2.9	5.2	3.6	2.7	2.9	3.7	3.6	3.5	3.0
Inter day Accuracy (%Actual)	0.6	-0.1	-3.0	0.3	0.5	1.0	0.0	0.0	0.0
Linearity	(0.9951 to 0.9996)								
Linearity Range (pg/mL)	5.00 to 500								
Sensitivity/LOQ (pg/mL)	5.00								

Bioequivalence Study No. AA31201 Analyte Name Scopolamine				
Parameter	**Quality Control Samples**			
Concentration (pg/mL)	15.0	50.0	150	375
Inter day Precision (%CV)	4.9	4.7	3.6	4.5
Inter day Accuracy (%Actual)	-2.7	-0.6	-2.0	-2.4

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. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
GL-BIO-10603-02	29-Dec-2005	Reporting of Data Generated from the Analysis of Biological Matrices and the Reassay of Samples

* SOP for Bioanalytical Repeats included in submission.

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No

Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

The only repeat assays performed in this study were due to unacceptable internal standard response (i.e., analytical reason). Five samples were repeated due to this reason.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 18 and Figure 1

Fasting Bioequivalence Study, Study No. AA31201									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *pg/ml)	6813	31.67	1369	10385	7276	25.84	3176	10413	0.94
AUC∞ (hr *pg/ml)	6960	30.66	1583	10519	7407	25.39	3297	10566	0.94
Cmax (pg/ml)	142.85	43.33	27.00	313.0	130.55	41.31	57.70	328.0	1.09
Tmax* (hr)	20.00	.	6.00	74.00	18.00	.	4.00	80.00	1.11
Kel (hr^{-1})	0.06	22.90	0.03	0.08	0.06	13.29	0.05	0.08	0.92
T1/2 (hr)	13.24	27.39	8.69	25.82	11.71	13.04	8.55	14.55	1.13

* Tmax values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Scopolamine 1.31 mg/72 hr Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. AA31201				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *pg/ml)	6377	7001	0.91	81.2-102.2
AUC∞ (hr *pg/ml)	6563	7168	0.92	82.2-102.0
Cmax (pg/ml)	128.44	121.85	1.05	92.0-120.7

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Scopolamine 1.31 mg/72 hr Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. AA31201					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *pg/ml)	6377	7001	0.91	81.22	102.16
AUC∞ (hr *pg/ml)	6554	7139	0.92	82.52	102.15
Cmax (pg/ml)	128.44	121.85	1.05	92.03	120.74

Table 17. Additional Study Information, Fasting Study No. AA31201

Root mean square error, AUC0-t	0.2516	
Root mean square error, AUC∞	0.2341	
Root mean square error, Cmax	0.2978	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	28	28
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	None	None
first measurable drug concentration as Cmax	None	None
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	28	0.97	0.86	0.99
Reference	28	0.98	0.95	0.99

Comments on Pharmacokinetic and Statistical Analysis:

For Subject No. 4, the time of the blood draw at the 48-hour time point in Period 1 is questionable. Hence an additional analysis was performed setting the concentration at this time point to missing. Reanalysis of the data set did not result in any change in the outcome of the study.

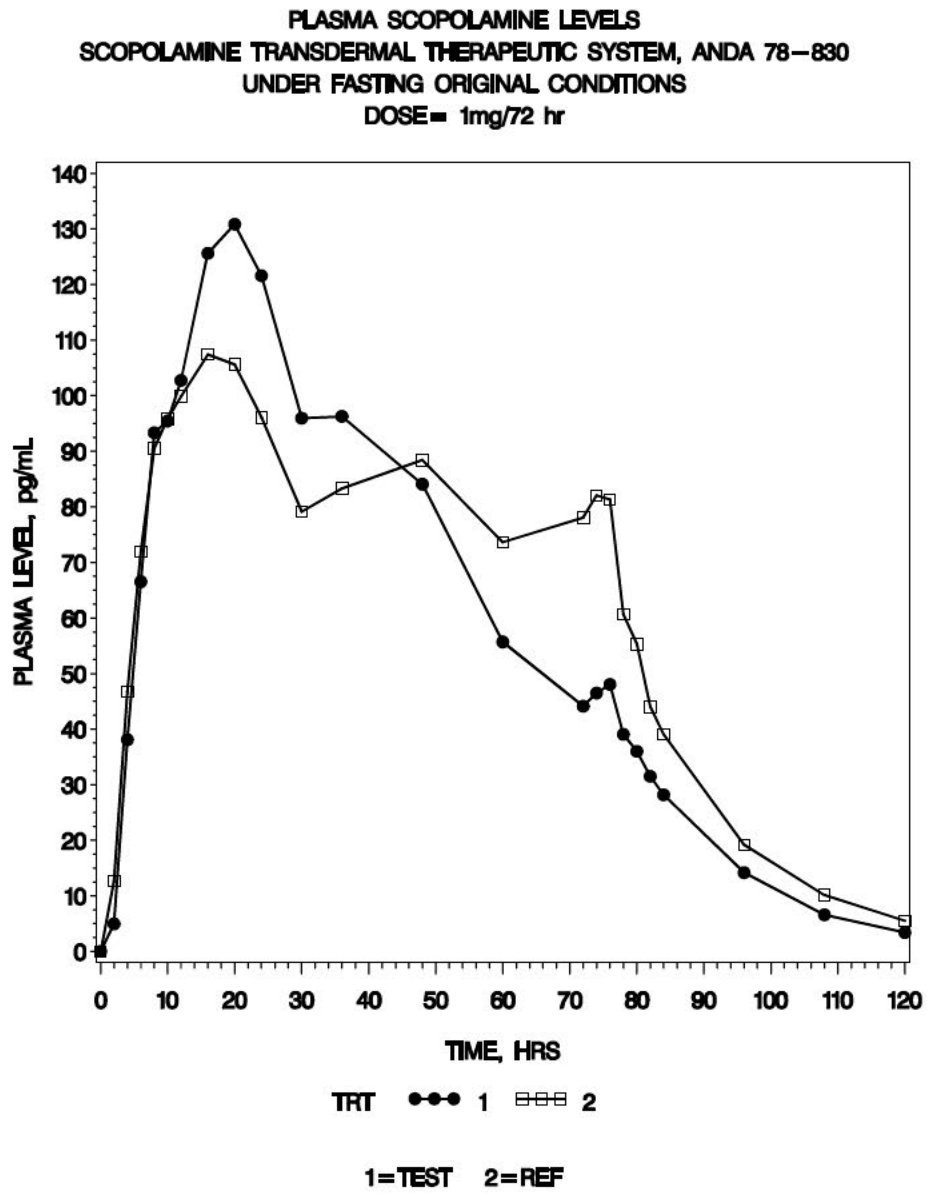
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The 90% confidence intervals for log-transformed AUCs and Cmax are entirely contained within the acceptable range of 80-125%. The study is considered acceptable.

Table 18. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	Test (n=28)		Reference (n=28)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
2.00	4.96	295.99	12.64	321.71	0.39
4.00	38.11	148.67	46.78	153.60	0.81
6.00	66.52	104.91	71.99	99.09	0.92
8.00	93.34	81.91	90.55	65.89	1.03
10.00	95.47	64.26	95.82	52.39	1.00
12.00	102.76	55.51	99.85	44.46	1.03
16.00	125.63	48.22	107.43	34.48	1.17
20.00	130.86	41.71	105.62	32.70	1.24
24.00	121.60	36.47	96.10	30.12	1.27
30.00	95.96	34.43	79.13	29.10	1.21
36.00	96.29	33.57	83.30	28.91	1.16
48.00	84.09	32.15	88.41	25.70	0.95
60.00	55.69	34.00	73.64	28.11	0.76
72.00	44.15	37.28	78.08	31.40	0.57
74.00	46.49	47.49	82.06	34.09	0.57
76.00	48.05	42.04	81.33	29.31	0.59
78.00	39.06	42.81	60.63	28.69	0.64
80.00	36.00	42.58	55.35	27.62	0.65
82.00	31.51	47.34	44.04	29.22	0.72
84.00	28.18	46.67	39.07	33.71	0.72
96.00	14.17	48.06	19.21	31.45	0.74
108.00	6.59	78.28	10.14	34.77	0.65
120.00	3.41	127.13	5.53	78.00	0.62

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



4.2 Formulation Data

Component	Component (as listed in labeling)	Component (as listed in Manufacturing Order	Reference	Role	mg/Unit Dose	% (w/w)
Scopolamine Base	Scopolamine	Scopolamine Base	(b) (4)	Active Ingredient	(b) (4)	(b) (4)

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:	None

(b) (4)

[redacted]

[5] Chemistry Review of ANDA-78830 (submission date: 23 Feb, 2007, Amendment 11 May, 2007)

Comments:

All the ingredients were found to be within IIG limits which have also been confirmed by chemistry review. (b) (4)

(b) (4)

(b) (4)

4.3 Dissolution Data

Dissolution Review Path	DFS

Table 19. Dissolution Data

Dissolution Conditions	**Apparatus:**	Apparatus 7 (reciprocating disks)
	Speed of Rotation:	(b) (4)
	Medium:	Distilled water
	Volume:	20 mL
	Temperature:	32.0 ± 0.3°C
	Stroke depth:	2 - 3 cm
	Dipping speed:	(b) (4)
Firm's Proposed Specifications	See Below	
Dissolution Testing Site (Name, Address)	Aveva Drug Delivery Systems, (b) (4) 3250 Commerce Parkway, Miramar, FL 33025	

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times 1 hr	2 hrs	4 hrs	6 hrs	24 hrs	48 hrs	72 hrs	Study Report Location
Perrigo Exhibit Batch: Scopolamine Transdermal Therapeutic System Lot # 35409, July 26, 2006	Transdermal Film, Extended Release – 1 mg/72 hr	12	Mean	41	44	48	50	69	91	105	Module 3, 3.2.P.2.2.1.3
			RSD (%)	4.7	2.2	1.9	2.1	3.6	4.2	3.8	
RLD: Transderm Scop® Lot # 20711701, Exp 08/2008	Transdermal Film, Extended Release – 1 mg/72 hr	12	Mean	28	35	40	43	63	85	105	Module 3, 3.2.P.2.2.1.3
			RSD (%)	6.1	3.6	2	1.8	1.6	1.5	1.5	
Firm's Proposed Specifications				(b) (4)							

Comments: On September 10, 2007, DBE (Reviewer: Svetlana Cherstniakova) completed review of the dissolution testing portion of the original ANDA submission dated February 23, 2007. The dissolution testing was incomplete and the firm was asked to provide dissolution data including individual data of drug release for the test and reference products for 12 units (Letter date: September 13, 2007). The firm submitted the amendment on 20 September, 2007. The dissolution review was completed on 10/30/2007. The review has accepted the dissolution results. However, the specifications as proposed by the firm were found to be unacceptable based on the data submitted and DBE has recommended different dissolution specifications. The firm was asked to acknowledge the acceptance of the specifications as recommended by DBE. Since the dissolution amendment review above was completed at approximately the same time as the current bioequivalence study review, the letter requesting the firm's acknowledgement of the proposed specifications will also be included in the current review and will be sent at the completion of the current bioequivalence review (instead of following the dissolution amendment review).

4.4 Detailed Regulatory History (If Applicable)

Per the review of the Control Document No. 050492 (Perrigo; submission date: 5/2/05), the Division of Bioequivalence (DBE) recommends the following to establish bioequivalence of scopolamine transdermal therapeutic system, 1 mg/72 hours:

1. The following study is recommended to establish bioequivalence of Scopolamine Transdermal Therapeutic System:

   A single-dose, two-way crossover fasting *in-vivo* bioequivalence study comparing Scopolamine Transdermal Therapeutic System to the reference listed drug (RLD), TRANSDERM SCŌP® (Scopolamine) Transdermal Therapeutic System. The transdermal system should be applied to the hairless area behind the ear. It may be necessary to use two transdermal systems, one behind each ear, to achieve measurable plasma concentrations. Study subjects in the single-dose bioequivalence study should wear the Scopolamine Transdermal Therapeutic System for 72 hours. The timing and frequency of sampling should adequately cover absorption, distribution, and elimination of the drug. If you determine that it is necessary to apply two transdermal systems to obtain adequate plasma concentrations, an Investigational New Drug Application (IND) is required (See 21 C.F.R. 320.31).

2. Because inactive components of a transdermal system could produce skin irritation or sensitization and could result in a generic product being more irritating than the reference product, skin irritation and sensitization studies are needed for all generic transdermal systems. In addition, adhesion performance must be evaluated to assure that the generic product has an acceptable adhesion performance.

3. Because safety concerns preclude the usual comparative studies, the OGD recommends evaluating generic scopolamine transdermal systems for skin irritation and sensitization by testing a placebo patch versus a positive and negative control patch. The placebo patch should have all of the inactive ingredients and be identical to your proposed product in every manner except for the absence of scopolamine. OGD has generally recommended that each patch be applied for the duration of wear that is recommended for the RLD (every 3 days) for 21 days.

4. The results of the skin irritation and sensitization studies should show that your proposed product is no more irritating than a positive control that produces mild irritation. Please also present a literature search on scopolamine hypersensitivity and skin reactions to scopolamine transdermal systems and any additional information you may have regarding controlled studies of scopolamine-induced irritation or contact sensitization to support that your proposed product is not likely to produce any greater degree of irritation or sensitization than that observed with use of the reference product.

5. The three properties – irritation, sensitization, and adhesion should be evaluated in the same study using separate analyses. Primary endpoint(s) for each of these analyses need to be clearly defined prior to the start of the study. The three primary endpoints should be considered as co-primary endpoints. In addition, the corresponding primary analysis for each primary endpoint needs to be specified. Secondary endpoint(s) (if any) need to be clearly defined prior to the start of the study.

6. It is recommended that the skin irritation and the skin sensitization evaluations are combined into a single study. Adhesion should be evaluated throughout the entire study period.

7. Scoring of skin reactions and patch adherence should be performed by a trained and blinded observer at each patch removal, using an appropriate scale. Dermal reactions should be scored on a scale that describes the amount of erythema, edema, and other features indicative of irritation. An example of an appropriate irritation scale is as follows:

DERMAL RESPONSE

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

0 = no other observations
1 = slight glazed appearance
2 = marked glazed appearance
3 = glazing with peeling and cracking
4 = glazing with fissures
5 = film of dried serous exudates covering all or part of the patch site
6 = small petechial erosions and/or scabs

8. As the irritation and adhesive properties may be sensitive to climate changes, we recommend that the study be conducted in multiple centers with varying climate conditions.

9. You should evaluate the percent adherence of the transdermal patches in these studies using an appropriate 5-point scale. The analysis should demonstrate that the adhesion of the proposed product. You should provide a chart showing the number of subjects with each adhesion score (0, 1, 2, 3, and 4) for each day of the study. The following scale is recommended for adhesion scoring:

   0 = ≥ 90% 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 by not detached (more than half the system lifting off of the skin without falling off)

   4 = patch detached (patch completely off the skin)

10. Reinforcement of the patches should not be allowed in the study

11. After three weeks of the irritation portion of the study (the induction phase of the sensitization study), there should be a two-week rest phase during which no patch applications are made. The rest phase should be followed by a challenge phase in which the patches are applied to a new skin site (different from the site used in the irritation phase) for 48 hours.

12. To be included in the sensitization analysis, patches should be evaluated by a trained and blinded observer at 30 minutes, and at 24, 48 and 72 hours after patch removal. Dermal reactions should be scored on a scale that describes the amount of erythema, edema, and other features indicative of sensitization.

13. The Population Definitions for the Per-Protocol (PP) evaluation for each parameter should be defined as follows:

    - Irritation Analysis– a patch needs to be worn for the entire 3 weeks to be evaluated for the cumulative irritation effect OR if a patch is removed due to irritation, it should be included using last observation carried forward (LOCF).
    - Adhesiveness Analysis – should include all patches except those removed early for unacceptable irritation
    - Sensitization Analysis – all patches worn for 48 hours during the challenge phase and returned for evaluation 24 hours post removal of the patch OR if patch removed prior to 48 hours due to a sensitization reaction, it should be included using LOCF.

14. The OGD is currently evaluating the appropriate statistical tests that should be used to analyze clinically meaningful differences between products with regard to skin irritation, sensitization and adhesion.

15. Please note that the guidance provided in this letter supersedes information provided in the Guidance for Industry: "Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products." The Guidance mentioned is currently under revision. Please be advised that the information given in this letter is general in nature. The OGD recommends that you submit protocols to the Clinical Review Team for review and comment **prior to** conducting the studies.

16. Please develop a method for determining in-vitro release of your product based on the USP 28 Transdermal Delivery Systems-General Drug Release Standards. Please conduct drug release testing on 12 individual dosage units. Sampling time intervals should be selected to characterize drug release from the system in its various performance phases such as start-up of the system to provide assurance against premature release of the drug, steady-state release, and cumulative drug release over the application period. A minimum of six different time points should be used to characterize drug release.

17. In addition, please perform the following dissolution test for your product:

Apparatus:	USP Apparatus 7 (reciprocating disk) Stroke of 2-3 cm at a rate of 30-60 cycles/minute
Dissolution vessels:	25 x 150 mm test-tubes containing 20 mL media
Media:	Distilled water
Temperature:	32 $\pm$ 0.3 degrees C
Sampling times:	1, 2, 4, 6, 24, 48, 72 hours

Tolerances will be determined upon review of the drug release data.

18. Please provide a table that identifies every missing sample in the study. Also, for every reassayed sample, please provide a table identifying the reason(s) for reassay, as well as the original and reassayed values of the sample. Please identify which value was selected for the PK analysis. Please provide the Standard Operating Procedures (SOPs) for all types of reassays including those that describe criteria for identifying and reassaying pharmacokinetically anomalous samples. The SOP(s) should clearly state objective criteria for defining pharmacokinetic anomalies, the method of reassay, and acceptance criteria for selecting which value to report for the reassayed sample. This SOP should be in place prior to the start of the study; otherwise, the Division of Bioequivalence may not accept reassayed values of samples. Finally, please conduct all pharmacokinetic and statistical analyses using both the original as well as reassayed values.

19. The bioequivalence data to be submitted in an ANDA should be provided in a diskette or CD in SAS Transport format in two separate files as described below:

    a. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE Thalf
    b. SUBJ SEQ PER TRT C1 C2 C3 …... . Cn

    Please separate each field with a blank space and indicate missing values with a period (.).

Please refer to the Guidance for Industry: "Providing Regulatory Submissions in Electronic Format-ANDAs" for information regarding the proper format at: www.fda.gov/cder/guidance/index.htm (under electronic submissions).

APPEARS THIS WAY ON ORIGINAL

4.5 SAS Output

4.5.1 Fasting Study Data

Obs	SUB	SEQ	PER	TREAT	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
1	(b) (6)	1	1	A	1	0	0.00	6.17	23.50	47.10	51.80	58.3	81.8	82.50	75.6	48.1	56.2	54.5	44.6	37.40
2		1	2	B	1	0	0.00	0.00	0.00	8.27	12.00	19.1	32.9	38.50	42.1	29.1	33.4	40.4	38.7	35.30
3		2	1	B	1	0	0.00	0.00	16.20	42.50	71.50	84.6	93.5	97.30	93.1	75.2	82.0	88.0	69.0	73.80
4		2	2	A	1	0	0.00	49.00	97.00	154.00	152.00	157.0	173.0	171.00	159.0	104.0	107.0	105.0	63.0	47.60
5		1	1	A	1	0	0.00	57.10	117.00	177.00	165.00	158.0	214.0	208.00	192.0	138.0	134.0	136.0	81.4	53.70
6		1	2	B	1	0	0.00	32.50	88.90	141.00	140.00	154.0	160.0	149.00	140.0	123.0	109.0	123.0	115.0	98.70
7		2	1	B	1	0	16.00	103.00	143.00	182.00	153.00	143.0	124.0	134.00	121.0	88.6	88.9	102.0	68.9	93.00
8		2	2	A	1	0	24.90	99.30	134.00	157.00	145.00	140.0	158.0	161.00	155.0	115.0	110.0	107.0	71.8	64.40
9		2	1	B	1	0	0.00	8.29	20.50	35.60	51.90	64.0	77.5	78.80	76.8	72.5	75.6	93.8	96.8	103.00
10		2	2	A	1	0	0.00	5.57	14.40	38.10	51.00	76.3	99.3	108.00	119.0	118.0	109.0	120.0	94.9	89.10
11		1	1	A	1	0	0.00	6.23	35.70	51.00	69.40	73.0	101.0	130.00	111.0	79.9	83.3	78.5	60.5	42.30
12		1	2	B	1	0	0.00	18.40	48.30	85.50	95.70	101.0	103.0	106.00	90.8	58.5	59.9	67.0	57.0	64.10
13		1	1	A	1	0	9.56	85.60	95.90	111.00	116.00	122.0	116.0	112.00	112.0	67.4	57.7	40.2	18.9	9.54
14		1	2	B	1	0	59.30	197.00	192.00	189.00	163.00	154.0	149.0	149.00	143.0	98.6	105.0	111.0	75.3	80.40
15		2	1	B	1	0	7.40	53.40	82.30	98.90	126.00	131.0	124.0	136.00	134.0	111.0	130.0	111.0	93.4	109.00
16		2	2	A	1	0	9.91	85.10	163.00	222.00	208.00	196.0	210.0	181.00	147.0	116.0	113.0	78.3	59.1	43.80
17		2	1	B	1	0	0.00	10.60	29.20	47.80	57.40	67.0	77.2	78.50	80.1	67.5	74.9	87.0	76.6	84.00
18		2	2	A	1	0	0.00	9.08	38.70	66.00	81.60	88.0	113.0	116.00	109.0	87.6	99.1	77.8	59.7	47.10
19		1	1	A	1	0	0.00	0.00	0.00	7.73	14.80	22.5	44.7	61.40	62.1	59.9	61.6	70.9	46.1	33.90
20		1	2	B	1	0	0.00	6.79	16.30	34.60	45.50	56.8	80.8	81.30	71.2	75.6	60.6	52.8	47.8	43.00
21		2	1	B	1	0	0.00	8.43	29.10	49.10	61.80	66.5	86.1	98.50	112.0	77.2	94.0	106.0	87.2	92.10
22		2	2	A	1	0	0.00	9.24	24.80	55.90	80.60	91.8	110.0	136.00	145.0	129.0	128.0	106.0	81.7	52.70

Obs	SUB	SEQ	PER	TREAT	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
23	(b) (6)	1	1	A	1	0	0.00	0.00	0.00	0.00	0.00	0.0	0.0	8.65	11.5	13.7	20.6	27.0	22.2	17.50
24		1	2	B	1	0	8.13	43.30	83.90	102.00	122.00	121.0	124.0	107.00	96.0	73.5	83.3	105.0	52.9	50.20
25		1	1	A	1	0	74.10	276.00	313.00	304.00	209.00	199.0	236.0	214.00	151.0	124.0	129.0	82.6	32.8	25.80
26		1	2	B	1	0	207.00	324.00	328.00	214.00	170.00	147.0	127.0	104.00	91.3	75.2	90.7	86.4	81.1	72.10
27		1	1	A	1	0	0.00	9.98	46.00	90.70	99.80	124.0	159.0	178.00	140.0	112.0	113.0	96.2	50.5	44.50
28		1	2	B	1	0	0.00	53.20	112.00	183.00	184.00	164.0	171.0	161.00	135.0	92.1	84.8	97.4	74.9	72.00
29		2	1	B	1	0	0.00	37.90	72.10	100.00	115.00	114.0	130.0	127.00	108.0	97.1	102.0	102.0	90.5	92.10
30		2	2	A	1	0	0.00	52.80	90.90	150.00	140.00	142.0	198.0	182.00	174.0	119.0	125.0	112.0	76.9	61.50
31		1	1	A	1	0	0.00	0.00	13.30	46.10	79.30	113.0	123.0	146.00	154.0	125.0	136.0	124.0	76.2	60.90
32		1	2	B	1	0	0.00	8.34	30.70	71.30	90.50	105.0	118.0	120.00	122.0	99.6	132.0	119.0	123.0	136.00
33		2	1	B	1	0	0.00	34.30	82.80	122.00	119.00	124.0	153.0	138.00	113.0	90.1	111.0	92.1	70.1	61.00
34		2	2	A	1	0	0.00	10.10	23.40	47.10	55.40	70.4	103.0	110.00	118.0	104.0	84.9	60.6	40.6	31.20
35		2	1	B	1	0	0.00	0.00	0.00	5.82	7.53	14.8	28.8	37.10	35.5	30.9	34.4	42.9	36.7	44.80
36		2	2	A	1	0	0.00	0.00	5.78	13.80	18.00	26.7	49.1	61.00	65.6	52.6	65.6	62.7	55.7	58.80
37		1	1	A	1	0	0.00	9.64	45.20	77.60	85.70	91.5	135.0	143.00	121.0	102.0	95.8	90.0	67.8	49.70
38		1	2	B	1	0	7.99	63.80	127.00	141.00	146.00	140.0	148.0	139.00	107.0	94.1	82.2	91.7	81.4	96.40
39		1	1	A	1	0	0.00	0.00	0.00	11.60	18.10	27.0	45.0	62.90	65.5	55.5	62.1	57.5	41.8	39.90
40		1	2	B	1	0	0.00	8.63	16.90	38.10	42.80	50.4	66.9	65.90	65.1	53.1	70.9	102.0	85.3	117.00
41		1	1	A	1	0	0.00	0.00	0.00	0.00	11.30	18.9	53.6	69.20	74.9	64.0	72.2	75.7	64.4	56.60
42		1	2	B	1	0	0.00	8.01	25.00	47.60	57.00	63.5	93.6	88.10	77.0	62.9	74.7	79.8	69.9	82.00
43		2	1	B	1	0	48.10	162.00	178.00	191.00	179.00	185.0	138.0	146.00	126.0	110.0	90.1	115.0	91.4	90.40
44		2	2	A	1	0	12.20	74.30	140.00	183.00	157.00	157.0	166.0	162.00	165.0	122.0	142.0	117.0	67.9	48.40
45		2	1	B	1	0	0.00	14.60	56.30	60.30	80.40	106.0	103.0	90.50	73.5	77.8	88.7	81.0	54.9	63.50
46		2	2	A	1	0	0.00	36.70	88.10	134.00	144.00	141.0	171.0	152.00	131.0	97.2	96.7	83.9	67.0	51.70
47		1	1	A	1	0	0.00	6.68	25.40	57.20	88.30	118.0	142.0	174.00	144.0	114.0	116.0	90.6	36.3	28.40
48		1	2	B	1	0	0.00	16.90	43.20	75.00	75.70	88.6	87.6	82.70	87.1	82.9	84.8	94.9	79.8	67.90

Obs	SUB	SEQ	PER	TREAT	GRP	c1	c2	c3	c4	c5	c6	c7	c8	c9	c10	c11	c12	c13	c14	c15
49	(b) (6)	2	1	B	1	0	0.00	8.32	21.00	41.20	54.70	65.5	90.9	85.50	82.8	70.7	67.6	57.1	51.1	54.00
50		2	2	A	1	0	0.00	6.17	10.00	16.30	20.90	33.9	54.3	64.10	72.9	67.7	71.3	65.5	53.0	49.60
51		1	1	A	1	0	0.00	78.20	136.00	182.00	181.00	186.0	206.0	230.00	199.0	161.0	160.0	109.0	54.8	39.10
52		1	2	B	1	0	0.00	51.50	78.20	102.00	120.00	113.0	142.0	153.00	115.0	109.0	101.0	88.7	72.7	99.90
53		2	1	B	1	0	0.00	18.30	63.90	92.40	103.00	111.0	126.0	110.00	103.0	76.0	78.7	89.5	69.1	66.90
54		2	2	A	1	0	0.00	36.70	101.00	138.00	144.00	157.0	164.0	156.00	146.0	114.0	79.1	80.9	43.5	31.20
55		2	1	B	1	0	0.00	18.30	30.80	34.50	38.60	42.1	52.3	55.60	49.5	43.7	42.2	49.1	51.4	43.70
56		2	2	A	1	0	8.32	57.40	80.60	75.30	86.10	89.1	91.8	84.30	84.6	76.4	67.9	45.1	26.1	19.90

Obs	c16	c17	c18	c19	c20	c21	c22	c23	c24
1	36.60	52.4	52.6	49.70	45.60	38.60	19.20	6.20	0.00
2	44.30	57.7	48.4	42.80	39.60	32.20	14.50	7.60	0.00
3	62.50	64.4	44.5	37.50	33.10	26.40	15.80	7.19	0.00
4	43.60	38.0	26.9	25.90	21.20	18.80	7.43	0.00	0.00
5	60.60	64.2	55.6	52.20	40.70	36.80	19.40	10.90	7.30
6	137.00	150.0	101.0	77.90	61.70	51.20	25.70	13.70	9.71
7	82.10	104.0	103.0	83.90	69.90	54.60	30.80	17.60	14.00
8	60.10	72.2	56.2	54.50	49.20	41.70	25.40	14.50	10.50
9	110.00	115.0	78.9	75.50	68.30	60.00	28.90	10.50	7.24
10	112.00	106.0	69.5	64.20	62.40	42.00	21.40	9.40	6.07
11	45.50	37.8	28.1	25.00	23.10	19.30	9.70	0.00	0.00
12	61.30	63.5	48.0	52.30	37.90	35.00	14.70	6.46	0.00
13	9.87	10.6	7.9	8.16	7.04	6.23	0.00	0.00	0.00
14	79.50	64.6	40.7	36.60	32.30	25.90	13.20	6.16	0.00
15	107.00	95.4	71.3	59.00	49.60	40.60	19.80	11.20	6.90
16	40.10	33.3	26.2	23.50	20.80	18.40	9.20	0.00	0.00
17	88.50	82.2	60.1	60.00	50.80	44.80	23.10	15.20	10.30
18	44.30	54.2	40.4	38.00	34.20	33.00	14.10	8.89	7.03
19	38.90	35.7	26.2	20.30	17.70	15.10	9.73	5.48	0.00
20	46.90	52.6	47.6	40.40	36.00	30.80	13.90	7.74	6.70
21	88.30	86.5	74.0	69.50	60.70	51.40	26.20	13.50	10.30
22	49.70	53.9	52.8	48.30	44.30	35.70	23.40	12.50	7.81
23	14.40	17.7	14.8	15.80	14.40	13.40	8.05	0.00	0.00
24	47.60	44.3	33.3	30.30	25.80	22.60	13.90	7.72	5.29
25	28.20	29.7	27.1	24.00	17.00	18.70	6.37	0.00	0.00
26	85.50	68.6	46.5	53.40	30.00	29.70	14.30	11.30	6.35
27	55.10	50.1	37.3	35.60	29.10	26.60	13.00	5.51	0.00
28	94.00	94.5	71.4	59.50	51.10	43.70	21.90	7.51	0.00
29	123.00	87.7	53.4	47.50	34.30	29.50	16.10	7.27	5.99
30	60.20	64.8	35.7	33.80	31.90	25.00	12.20	7.03	0.00
31	80.20	61.2	49.0	40.30	36.70	32.40	16.70	8.62	6.23
32	139.00	113.0	84.0	69.90	57.00	53.10	21.10	12.40	8.15
33	56.80	67.7	55.7	47.90	37.90	32.20	20.80	10.50	8.45
34	29.60	34.6	26.8	26.30	20.90	20.80	14.10	7.86	6.09
35	38.30	56.8	42.5	72.20	42.80	43.70	23.40	11.90	8.72
36	84.60	81.3	65.3	63.40	54.80	42.60	19.10	10.00	6.02
37	56.20	64.0	67.0	51.30	38.60	35.50	13.20	6.45	0.00

Obs	c16	c17	c18	c19	c20	c21	c22	c23	c24
38	102.00	103.0	64.4	59.30	37.70	31.20	11.60	5.79	0.00
39	26.70	38.8	35.3	34.90	29.20	30.10	22.70	15.40	12.30
40	107.00	105.0	66.5	61.90	41.20	38.80	18.80	12.10	8.01
41	57.00	56.1	57.0	61.40	63.90	71.50	30.50	17.80	13.10
42	79.30	87.9	77.6	85.70	71.50	83.20	34.90	19.40	12.50
43	93.50	69.5	46.0	38.50	31.70	25.10	12.10	5.66	0.00
44	52.60	48.1	36.4	32.80	26.20	22.40	13.20	5.99	0.00
45	75.20	72.6	61.2	53.20	46.80	40.20	21.20	10.80	6.57
46	55.20	44.3	30.3	25.50	23.90	21.70	10.40	0.00	0.00
47	26.00	36.0	28.8	30.70	21.10	21.80	8.89	6.22	0.00
48	79.00	65.1	50.9	37.50	32.60	27.10	12.50	7.85	0.00
49	47.20	64.3	54.0	53.30	37.60	36.10	17.40	10.70	6.23
50	48.70	58.1	60.6	51.50	47.80	41.80	19.20	10.30	7.67
51	41.70	51.9	38.1	29.70	26.70	25.90	14.60	8.67	5.42
52	107.00	107.0	70.2	61.70	43.30	40.60	18.90	9.81	7.02
53	65.40	62.3	54.0	40.10	38.90	30.20	13.60	6.46	0.00
54	28.10	28.2	21.9	20.70	17.10	14.90	6.66	0.00	0.00
55	50.40	72.1	48.6	42.60	32.90	34.00	18.70	9.95	6.31
56	16.00	22.2	20.0	20.60	16.70	18.20	9.04	6.82	0.00

4.5.2 Fasting Study Output

Obs	SUB	TRT	SEQ	PER	GRP	auct	auci	CMAX	TMAX	THALF	kel
1	(b) (6)	1	1	1	1	4724.24	4807.13	82.5	20.0	9.2664	0.074802
2		2	1	2	1	3176.04	3302.37	57.7	76.0	11.5220	0.060159
3		1	2	2	1	7969.58	8066.11	173.0	16.0	9.0056	0.076968
4		2	2	1	1	6234.24	6362.78	97.3	20.0	12.3919	0.055936
5		1	1	1	1	10384.50	10542.38	214.0	16.0	14.9912	0.046237
6		2	1	2	1	10413.36	10620.81	160.0	16.0	14.8086	0.046807
7		1	2	2	1	9285.90	9554.10	161.0	20.0	17.7050	0.039150
8		2	2	1	1	9226.30	9588.17	182.0	8.0	17.9164	0.038688
9		1	2	2	1	8290.96	8400.90	120.0	48.0	12.5540	0.055213
10		2	2	1	1	7389.02	7507.12	115.0	76.0	11.3065	0.061305
11		1	1	1	1	5728.16	5891.13	130.0	20.0	11.6453	0.059521
12		2	1	2	1	5901.76	5993.51	106.0	20.0	9.8451	0.070405
13		1	1	1	1	4467.17	4559.51	122.0	12.0	10.2737	0.067468
14		2	1	2	1	9188.66	9291.60	197.0	4.0	11.5833	0.059840

Obs	SUB	TRT	SEQ	PER	GRP	auct	auci	CMAX	TMAX	THALF	kel
15	(b) (6)	1	2	2	1	8403.22	8561.59	222.0	8.0	11.9320	0.058092
16		2	2	1	1	9353.00	9510.09	136.0	20.0	15.7808	0.043923
17		1	2	2	1	6484.22	6726.64	116.0	20.0	23.9021	0.028999
18		2	2	1	1	6662.80	6968.86	88.5	74.0	20.5963	0.033654
19		1	1	1	1	3935.50	4061.51	70.9	48.0	15.9391	0.043487
20		2	1	2	1	4850.86	4995.20	81.3	20.0	14.9327	0.046418
21		1	2	2	1	8098.34	8279.05	145.0	24.0	16.0382	0.043219
22		2	2	1	1	7723.06	7937.09	112.0	24.0	14.4038	0.048123
23		1	1	1	1	1368.90	1560.60	27.0	48.0	16.5067	0.041992
24		2	1	2	1	6734.54	6860.05	124.0	16.0	16.4452	0.042149
25		1	1	1	1	9395.72	9475.69	313.0	6.0	8.7019	0.079655
26		2	1	2	1	9210.90	9367.58	328.0	6.0	17.1023	0.040529
27		1	1	1	1	7463.52	7547.52	178.0	20.0	10.5666	0.065598
28		2	1	2	1	8801.56	8906.22	184.0	10.0	9.6598	0.071756
29		1	2	2	1	9036.08	9169.07	198.0	16.2	13.1124	0.052862
30		2	2	1	1	8229.98	8353.87	130.0	16.0	14.3367	0.048348
31		1	1	1	1	8367.92	8501.24	154.0	24.0	14.8328	0.046731
32		2	1	2	1	9668.68	9874.30	139.0	74.0	17.4880	0.039636
33		1	2	2	1	5468.16	5639.33	118.0	24.0	19.4827	0.035578
34		2	2	1	1	7913.90	8129.79	153.0	16.0	17.7088	0.039141
35		1	2	2	1	5044.38	5155.22	84.6	74.0	12.7624	0.054312
36		2	2	1	1	3563.02	3752.88	72.2	80.0	15.0920	0.045928
37		1	1	1	1	7143.28	7234.05	143.0	20.0	9.7543	0.071061
38		2	1	2	1	8256.12	8335.93	148.0	16.0	9.5549	0.072544
39		1	1	1	1	4333.80	4814.16	65.5	24.0	27.0693	0.025606
40		2	1	2	1	6697.72	6923.05	117.0	72.0	19.4986	0.035548
41		1	1	1	1	5805.70	6177.72	75.7	48.0	19.6844	0.035213
42		2	1	2	1	7110.62	7402.80	93.6	16.0	16.2020	0.042782
43		1	2	2	1	9051.94	9160.78	183.0	8.0	12.5946	0.055035
44		2	2	1	1	9330.96	9422.16	191.0	8.0	11.1690	0.062060
45		1	2	2	1	7374.50	7547.60	171.0	16.0	11.5367	0.060082
46		2	2	1	1	6545.92	6674.99	106.0	12.0	13.6167	0.050904
47		1	1	1	1	6724.56	6843.59	174.0	20.0	13.2645	0.052256
48		2	1	2	1	6553.40	6696.56	94.9	48.0	12.6405	0.054835
49		1	2	2	1	5089.66	5250.87	72.9	24.0	14.5683	0.047579
50		2	2	1	1	5415.62	5561.19	90.9	16.0	16.1966	0.042796
51		1	1	1	1	9965.96	10090.71	230.0	20.0	15.9540	0.043447

Obs	SUB	TRT	SEQ	PER	GRP	auct	auci	CMAX	TMAX	THALF	kel
52	(b) (6)	2	1	2	1	8445.74	8588.02	153.0	20.0	14.0485	0.049340
53		1	2	2	1	6803.76	6902.77	164.0	16.0	10.3045	0.067267
54		2	2	1	1	6817.76	6918.29	126.0	16.0	10.7868	0.064259
55		1	2	2	1	4541.14	4707.90	91.8	16.0	16.9480	0.040898
56		2	2	1	1	4316.56	4449.78	72.1	76.0	14.6346	0.047364

FASTING ORIGINAL STATISTICAL OUTPUT

The GLM Procedure

Class Level Information		
Class	**Levels**	**Values**
SUB	28	1 2 4 5 6 7 8 9 10 11 12 13 14 15 16 18 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	56
Number of Observations Used	56

FASTING ORIGINAL STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	29	5.46788666	0.18854782	2.98	0.0031
Error	26	1.64580533	0.06330020		
Corrected Total	55	7.11369199			

R-Square	Coeff Var	Root MSE	LAUCT Mean
0.768643	2.856717	0.251595	8.807150

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.06613499	0.06613499	1.04	0.3161
SUB(SEQ)	26	5.06512909	0.19481266	3.08	0.0028
PER	1	0.21469924	0.21469924	3.39	0.0770
TRT	1	0.12192335	0.12192335	1.93	0.1770

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.06613499	0.06613499	1.04	0.3161
SUB(SEQ)	26	5.06512909	0.19481266	3.08	0.0028
PER	1	0.21469924	0.21469924	3.39	0.0770
TRT	1	0.12192335	0.12192335	1.93	0.1770

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	0.06613499	0.06613499	0.34	0.5651

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.09332101	0.06724168	-1.39	0.1770

FASTING ORIGINAL STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LAUCI

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	29	5.04931542	0.17411432	3.18	0.0019
Error	26	1.42540925	0.05482343		
Corrected Total	55	6.47472467			

R-Square	Coeff Var	Root MSE	LAUCI Mean
0.779850	2.651519	0.234144	8.830563

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.05519271	0.05519271	1.01	0.3249
SUB(SEQ)	26	4.70742131	0.18105467	3.30	0.0017
PER	1	0.18450957	0.18450957	3.37	0.0780
TRT	1	0.10219184	0.10219184	1.86	0.1839

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.05519271	0.05519271	1.01	0.3249
SUB(SEQ)	26	4.70742131	0.18105467	3.30	0.0017
PER	1	0.18450957	0.18450957	3.37	0.0780
TRT	1	0.10219184	0.10219184	1.86	0.1839

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	0.05519271	0.05519271	0.30	0.5856

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	-0.08543663	0.06257763	-1.37	0.1839

FASTING ORIGINAL STATISTICAL OUTPUT

The GLM Procedure

Dependent Variable: LCMAX

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	29	8.31318715	0.28666163	3.23	0.0017
Error	26	2.30621994	0.08870077		
Corrected Total	55	10.61940709			

R-Square	Coeff Var	Root MSE	LCMAX Mean
0.782830	6.167309	0.297827	4.829120

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SEQ	1	0.00021263	0.00021263	0.00	0.9613
SUB(SEQ)	26	8.03853689	0.30917450	3.49	0.0011
PER	1	0.23557359	0.23557359	2.66	0.1152
TRT	1	0.03886404	0.03886404	0.44	0.5138

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SEQ	1	0.00021263	0.00021263	0.00	0.9613
SUB(SEQ)	26	8.03853689	0.30917450	3.49	0.0011
PER	1	0.23557359	0.23557359	2.66	0.1152
TRT	1	0.03886404	0.03886404	0.44	0.5138

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	0.00021263	0.00021263	0.00	0.9793

Parameter	Estimate	Standard Error	t Value	Pr > |t|
TRT1 VS TRT2	0.05268779	0.07959754	0.66	0.5138

78-830 FASTING ORIGINAL FIRM TO REVIEWER RATIO

Obs	SUB	SEQ	PER	GRP	TRT	FDAAREA	FDAAUCI	FDACMAX	TREAT	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
1	(b) (6)	1	1	1	1	4724.24	4807.13	82.5	A	4724.24	4807.13	82.5	1.00000	1.00000	1
2		1	2	1	2	3176.04	3302.37	57.7	B	3176.04	3302.37	57.7	1.00000	1.00000	1
3		2	2	1	1	7969.58	8066.11	173.0	A	7969.58	8066.11	173.0	1.00000	1.00000	1
4		2	1	1	2	6234.24	6362.78	97.3	B	6234.24	6362.78	97.3	1.00000	1.00000	1
5		1	1	1	1	10384.50	10542.38	214.0	A	10394.34	10552.22	214.0	1.00095	1.00093	1
6		1	2	1	2	10413.36	10620.81	160.0	B	10413.36	10620.81	160.0	1.00000	1.00000	1
7		2	2	1	1	9285.90	9554.10	161.0	A	9285.90	9554.10	161.0	1.00000	1.00000	1
8		2	1	1	2	9226.30	9588.17	182.0	B	9226.30	9588.17	182.0	1.00000	1.00000	1
9		2	2	1	1	8290.96	8400.90	120.0	A	8290.96	8400.90	120.0	1.00000	1.00000	1
10		2	1	1	2	7389.02	7507.12	115.0	B	7389.02	7507.12	115.0	1.00000	1.00000	1
11		1	1	1	1	5728.16	5891.13	130.0	A	5728.16	5891.13	130.0	1.00000	1.00000	1
12		1	2	1	2	5901.76	5993.51	106.0	B	5901.76	5993.51	106.0	1.00000	1.00000	1
13		1	1	1	1	4467.17	4559.51	122.0	A	4467.17	4559.51	122.0	1.00000	1.00000	1
14		1	2	1	2	9188.66	9291.60	197.0	B	9190.95	9293.89	197.0	1.00025	1.00025	1
15		2	2	1	1	8403.22	8561.59	222.0	A	8403.22	8561.59	222.0	1.00000	1.00000	1
16		2	1	1	2	9353.00	9510.09	136.0	B	9353.00	9510.09	136.0	1.00000	1.00000	1
17		2	2	1	1	6484.22	6726.64	116.0	A	6484.22	6726.64	116.0	1.00000	1.00000	1
18		2	1	1	2	6662.80	6968.86	88.5	B	6662.80	6968.86	88.5	1.00000	1.00000	1
19		1	1	1	1	3935.50	4061.51	70.9	A	3935.50	4061.51	70.9	1.00000	1.00000	1
20		1	2	1	2	4850.86	4995.20	81.3	B	4849.38	4993.72	81.3	0.99969	0.99970	1
21		2	2	1	1	8098.34	8279.05	145.0	A	8098.34	8279.05	145.0	1.00000	1.00000	1
22		2	1	1	2	7723.06	7937.09	112.0	B	7723.06	7937.10	112.0	1.00000	1.00000	1
23		1	1	1	1	1368.90	1560.60	27.0	A	1368.90	1560.60	27.0	1.00000	1.00000	1
24		1	2	1	2	6734.54	6860.05	124.0	B	6734.54	6860.05	124.0	1.00000	1.00000	1
25		1	1	1	1	9395.72	9475.69	313.0	A	9391.03	9471.00	313.0	0.99950	0.99950	1
26		1	2	1	2	9210.90	9367.58	328.0	B	9205.72	9362.39	328.0	0.99944	0.99945	1
27		1	1	1	1	7463.52	7547.52	178.0	A	7463.52	7547.52	178.0	1.00000	1.00000	1
28		1	2	1	2	8801.56	8906.22	184.0	B	8801.56	8906.22	184.0	1.00000	1.00000	1
29		2	2	1	1	9036.08	9169.07	198.0	A	9032.10	9165.09	198.0	0.99956	0.99957	1
30		2	1	1	2	8229.98	8353.87	130.0	B	8227.81	8351.70	130.0	0.99974	0.99974	1
31		1	1	1	1	8367.92	8501.24	154.0	A	8367.92	8501.24	154.0	1.00000	1.00000	1
32		1	2	1	2	9668.68	9874.30	139.0	B	9668.68	9874.30	139.0	1.00000	1.00000	1
33		2	2	1	1	5468.16	5639.33	118.0	A	5468.16	5639.33	118.0	1.00000	1.00000	1
34		2	1	1	2	7913.90	8129.79	153.0	B	7913.90	8129.78	153.0	1.00000	1.00000	1
35		2	2	1	1	5044.38	5155.22	84.6	A	5044.07	5154.91	84.6	0.99994	0.99994	1
36		2	1	1	2	3563.02	3752.88	72.2	B	3563.02	3752.88	72.2	1.00000	1.00000	1
37		1	1	1	1	7143.28	7234.05	143.0	A	7143.28	7234.05	143.0	1.00000	1.00000	1
38		1	2	1	2	8256.12	8335.93	148.0	B	8256.12	8335.93	148.0	1.00000	1.00000	1

Obs	SUB	SEQ	PER	GRP	TRT	FDAAREA	FDAAUCI	FDACMAX	TREAT	FIRMAREA	FIRMAUCI	FIRMCMAX	RAUCT	RAUCI	RCMAX
39	(b) (6)	1	1	1	1	4333.80	4814.16	65.5	A	4333.80	4814.15	65.5	1.00000	1.00000	1
40		1	2	1	2	6697.72	6923.05	117.0	B	6697.10	6922.43	117.0	0.99991	0.99991	1
41		1	1	1	1	5805.70	6177.72	75.7	A	5805.70	6177.72	75.7	1.00000	1.00000	1
42		1	2	1	2	7110.62	7402.80	93.6	B	7111.68	7403.86	93.6	1.00015	1.00014	1
43		2	2	1	1	9051.94	9160.78	183.0	A	9051.94	9160.78	183.0	1.00000	1.00000	1
44		2	1	1	2	9330.96	9422.16	191.0	B	9330.96	9422.16	191.0	1.00000	1.00000	1
45		2	2	1	1	7374.50	7547.60	171.0	A	7374.50	7547.60	171.0	1.00000	1.00000	1
46		2	1	1	2	6545.92	6674.99	106.0	B	6545.92	6674.99	106.0	1.00000	1.00000	1
47		1	1	1	1	6724.56	6843.59	174.0	A	6724.56	6843.59	174.0	1.00000	1.00000	1
48		1	2	1	2	6553.40	6696.56	94.9	B	6553.40	6696.56	94.9	1.00000	1.00000	1
49		2	2	1	1	5089.66	5250.87	72.9	A	5089.66	5250.86	72.9	1.00000	1.00000	1
50		2	1	1	2	5415.62	5561.19	90.9	B	5415.62	5561.20	90.9	1.00000	1.00000	1
51		1	1	1	1	9965.96	10090.71	230.0	A	9965.96	10090.71	230.0	1.00000	1.00000	1
52		1	2	1	2	8445.74	8588.02	153.0	B	8445.74	8588.02	153.0	1.00000	1.00000	1
53		2	2	1	1	6803.76	6902.77	164.0	A	6803.76	6902.77	164.0	1.00000	1.00000	1
54		2	1	1	2	6817.76	6918.29	126.0	B	6817.76	6918.29	126.0	1.00000	1.00000	1
55		2	2	1	1	4541.14	4707.90	91.8	A	4541.14	4707.90	91.8	1.00000	1.00000	1
56		2	1	1	2	4316.56	4449.78	72.1	B	4316.56	4449.78	72.1	1.00000	1.00000	1

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78830

APPLICANT: Perrigo Pharmaceuticals

DRUG PRODUCT: Scopolamine Transdermal System, 1 mg/72 hr

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

Your dissolution data as submitted using the following FDA-recommended dissolution method are acceptable:

The dissolution testing should be conducted in 25 x 150 mm test tubes containing 20 mL of distilled water at 32°C ± 0.3°C using USP apparatus 7 (reciprocating disk) at a stroke of 2-3 cm at a rate of 30-60 cycles/minute.

However, based on the data submitted, your proposed dissolution specifications are not acceptable. Please acknowledge your acceptance of the following DBE-recommended dissolution specifications:

6 hr: (b) (4) %
24 hr: (b) (4) %
48 hr: (b) (4) %
72 hr: (b) (4) %

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.6 Outcome Page

ANDA: 78830

Reviewer: Mandula, Haritha **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
919	2/23/2007	Bioequivalence Study	Fasting Study	1	1
919	9/20/2007	Other	Study Amendment Without Credit (WC)	0	0
				Bean 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/

Haritha Mandula
11/27/2007 09:30:55 AM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
11/27/2007 09:39:15 AM
BIOPHARMACEUTICS

Barbara Davit
11/27/2007 06:25:04 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW OF DISSOLUTION AMENDMENT

ANDA No.	78830
Drug Product Name	Scopolamine Transdermal Therapeutic System
Strength (s)	1 mg /72 hours
Applicant Name	Perrigo R&D Company
Address	515 Eastern Ave. Allegan, MI 49010
Applicant's Point of Contact	Valerie Gallagher
Contact's Phone Number	(269) 673-8451
Contact's Fax Number	(269) 673-7655
Submission Date(s) **Submission Date(s) of Amendment(s)**	23 February 2007 20 September 2007
First Generic	Yes
Reviewer	Svetlana Cherstniakova, Ph.D.
Study Number (s) **Study Type (s)** **Strength (s)**	AA31201 Transdermal Delivery System 0.15 mg / 0.02 mg /24 hours
Clinical Site	MDS Pharma Services
Clinical Address	2350 Cohen Street Saint-Laurent, Montreal Quebec, H4R 2N6 Canada
Analytical Site	(b) (4)
Analytical Address	

I. EXECUTIVE SUMMARY

The firm has submitted this amendment in response to DBE deficiency following dissolution review. The application was incomplete due to inadequate dissolution data (see DFS N 078830 N 000 23-Feb-2007). In this amendment the firm has responded to the deficiencies.

There is no USP method for this product. The firm has used dissolution method per DBE recommendation provided in a recent control correspondence (OGD # 05-1125, Perrigo Company). The method uses USP Apparatus 7 (reciprocating disk), with Stroke of 2-3 cm at a rate of 30-60 cycles/minute, 20 mL distilled water as the dissolution medium and sampling times 1, 2, 4, 6, 24, 48, 72 hours. The dissolution testing was conducted on 12 units each of the test and reference products. The firm has proposed dissolution specifications for its test product as follows:

Proposed Specifications (%TDR)	1 hour	2 hour	4 hour	6 hour	24 hour	48 hour	72 hour
	(b) (4)						

The firm's proposed specifications for its test product are not acceptable. Based on the submitted data, the DBE recommends the following specifications:

6hr: (b) (4)%
24 hr: %
48 hr: (b) (4)%
72 hr: %

The dissolution testing is incomplete pending firm's acknowledgement of the DBE-recommended dissolution specifications.

The DBE will review the fasting BE study at a later date.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended 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	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are all eight electronic summary biotables present			☒	☐	☐
Are electronic summary biotables in pdf format			☒	☐	☐

Comments:

The firm performed one BE study on the 1 mg /72 hours Scopolamine Transdermal Patch and measured scopolamine, calculating the 90% CI for the analyte. The BE tables are on the EDR.

II. DISSOLUTION DATA

FDA-recommended method (OGD # 05-1125, Perrigo Company):

With respect to the dissolution testing on the Scopolamine Transdermal Therapeutic System, 1 mg/72 hours, the Office of Generic Drugs (OGD) provided the following recommendation to Perrigo through a control correspondence OGD # 05-1125:

- Please develop a method for determining in-vitro release of your product based on the USP 28 Transdermal Delivery Systems-General Drug Release Standards. Please conduct drug release testing on 12 individual dosage units. Sampling time intervals should be selected to characterize drug release from the system in its various performance phases such as start-up of the system to provide assurance against premature release of the drug, steady-state release, and cumulative drug release over the application period. A minimum of six different time points should be used to characterize drug release.

- In addition, please perform the following dissolution test for your product:

Apparatus:	USP Apparatus 7 (reciprocating disk)
	Stroke of 2-3 cm at a rate of 30-60 cycles/minute
Dissolution vessels:	25 x 150 mm test-tubes containing 20 mL media
Media:	Distilled water
Temperature:	32 + 0.3 ºC
Sampling times:	1, 2, 4, 6, 24, 48, 72 hours

Tolerances will be determined upon review of the drug release data.

In supplement's review (SCM-030) to NDA 17-874 dated July 2, 2002, the following specifications* for the percent of scopolamine released with time are recommended for Transderm Scop®(scopolamine) Transdermal Therapeutic System:

Percent of Drug Released	
Sampling Time	**Specification**
6 hour	(b) (4)%
12 hour	%
24 hour	%
48 hour	%
72 hour	%

*The recommended specifications are based on the mean ± 10% values. It is further noted that in the NDA 17874 review, the collection of additional data at 0-2 and 2-6 hours was not recommended due the fact that transderm scopolamine system presents a bi-phasic release profile in which the first phase is approximately from 0-12 hours.

The firm has used dissolution method as recommended by the OGD.

Drug Release Conditions	
Apparatus:	USP <724> Apparatus 7 (reciprocating disks)
Dissolution medium:	Distilled water
Release volume:	20 mL
Bath temperature:	32.0 ± 0.3°C
Stroke depth:	2 - 3 cm
Dipping speed:	45 dpm
Sampling times:	1, 2, 4, 6, 24, 48, and 72 hours.
Number of patches tested:	12

The dissolution results are summarized in the Tables below.

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Batch Name / Lot #	Time (Hour)	0	1	2	4	6	24	48	72
Exhibit Batch / 35409	Average Drug Release (%TDR)	0	41	44	48	50	69	91	105
	RSD (%)	0	4.7	2.2	1.9	2.1	3.6	4.2	3.8
Transderm Scop® Lot#20711701, Exp. 08/2008	Average Drug Release (%TDR)	0	28	35	40	43	63	85	105
	RSD (%)	0	6.1	3.6	2	1.8	1.6	1.5	1.5
[redacted]						(b) (4)			

In response to the DBE deficiency in the original dissolution review, the firm has submitted individual dissolution data summarized in the following Table.

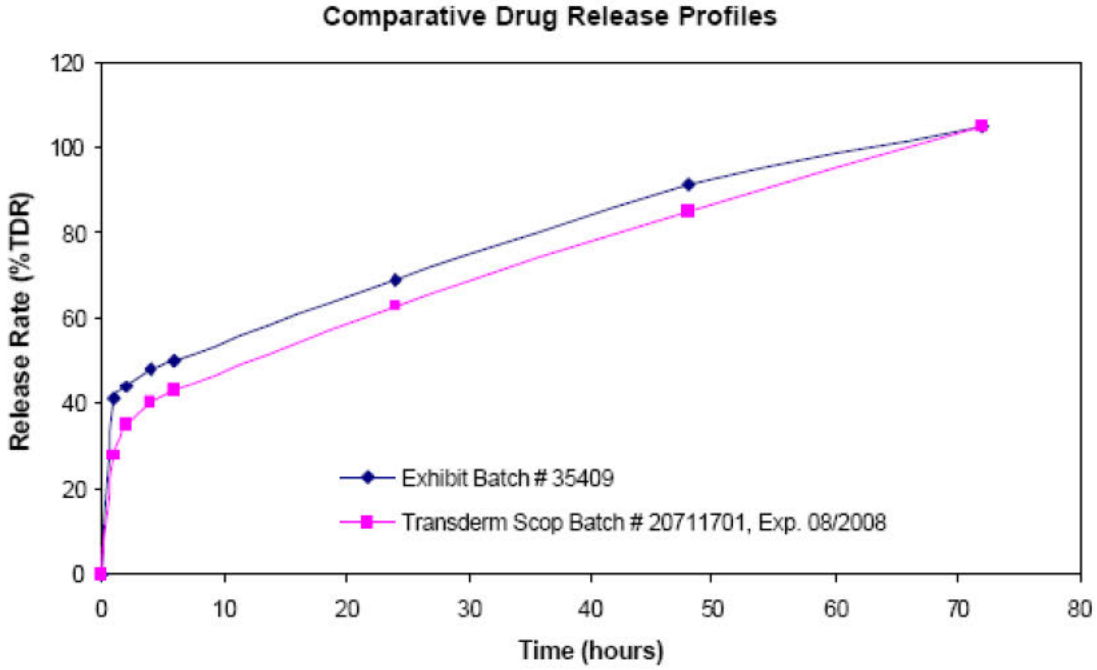
Product ID \ Batch No.	Dosage Strength & Form		Collection Times (hours)						
			1 hour	2 hour	4 hour	6 hour	24 hour	48 hour	72 hour
Exhibit Batch # 35409	Transdermal System, 1.0 mg/ 3 days	1	(b) (4)						
		2							
		3							
		4							
		5							
		6							
		7							
		8							
		9							
		10							
		11							
		12							
		Mean	41	44	48	50	69	91	105
		Range	(b) (4)						
		%CV	4.7	2.2	1.9	2.1	3.6	4.2	3.8

(b) (4)

Product ID \ Batch No.	Dosage Strength & Form		Collection Times (hours)						
			1 hour	2 hour	4 hour	6 hour	24 hour	48 hour	72 hour
Transderm Scop Lot #20711701, Exp. 08/2008	Transdermal System, 1.0 mg/ 3 days	1	(b) (4)						
		2							
		3							
		4							
		5							
		6							
		7							
		8							
		9							
		10							
		11							
		12							
		Mean	28	35	40	43	63	85	105
		Range	(b) (4)						
		%CV	6.1	3.6	2.0	1.8	1.6	1.5	1.5

(b) (4)

Comparative Dissolution Profiles



The firm has proposed the following specifications:

Proposed Specifications (%TDR)	1 hour	2 hour	4 hour	6 hour	24 hour	48 hour	72 hour
	(b) (4)						

COMMENTS

Currently, the OGD Dissolution Data Base does not provide any dissolution method on scopolamine.

The firm has used dissolution testing on 12 individual dosage units of the test and reference product, and 6 different time points to characterize drug release per the OGD recommendation in the control correspondence (OGD # 05-1125, Perrigo Company). It is noted that the OGD recommended method is very similar to that in the NDA method described above.

The firm's dissolution testing data using the DBE-recommended method are acceptable. As shown below, the firm's proposed specifications* are different from those recommended for Transderm Scop®(scopolamine) Transdermal Therapeutic System:

Firms Proposed Specifications	RLD Specifications**
6 hr: (b) (4)%	6hr: (b) (4)%
12 hr: -	12 hr: (b) (4)%
24 hr: (b) (4) 6%	24 hr: (b) (4)%
48 hr: (b) (4)%	48 hr: (b) (4)%
72 hr: (b) (4)%	72 hr: (b) (4)%

* Percent of scopolamine released with time
** The recommended specifications are based on the mean ± 10% values

Based on the submitted data, the DBE recommends the following dissolution specifications:

6hr: (b) (4)%
24 hr: %
48 hr: (b) (4)%
72 hr: %

The firm should acknowledge the DBE-recommended dissolution specifications.

III. DEFICIENCY COMMENTS

The firm's proposed specifications are not acceptable. Based on the submitted data, the DBE recommends the following dissolution specifications:

6hr: (b) (4)%
24 hr: %
48 hr: (b) (4)%
72 hr: %

IV. RECOMMENDATIONS

The dissolution testing conducted by Perrigo Company on the test product, Scopolamine Transdermal Patch, 1 mg /72 hours Lot # 35409, is incomplete due to the reasons given in the deficiency comments.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78830

APPLICANT: Perrigo R&D Company

DRUG PRODUCT: Scopolamine Transdermal Patch, 1 mg /72 hours

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The following deficiency has been identified:

Your dissolution results using the following dissolution method are acceptable:

Apparatus:	USP Apparatus 7 (reciprocating disk) Stroke of 2-3 cm at a rate of 30-60 cycles/minute
Dissolution vessels:	25 x 150 mm test-tubes containing 20 mL media
Media:	Distilled water
Temperature:	32 ± 0.3 °C
Sampling times:	1, 2, 4, 6, 24, 48, 72 hours

However, based on the data submitted, your dissolution specifications are not acceptable. Please acknowledge your acceptance of the following DBE-recommended dissolution specifications:

6hr:	(b) (4) %
24 hr:	%
48 hr:	(b) (4) %
72 hr:	%

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

V. OUTCOME

Completed Assignment for 78830 ID: 667

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
667	9/20/2007	Dissolution Data	Dissolution Amendment	1	1

APPEARS THIS WAY ON ORIGINAL

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/s/

Svetlana Cherstniakova
10/30/2007 08:18:13 AM
BIOPHARMACEUTICS

Chandra S. Chaurasia
10/30/2007 09:43:30 AM
BIOPHARMACEUTICS

Barbara Davit
10/30/2007 04:26:39 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	78830
Drug Product Name	Scopolamine Transdermal Therapeutic System
Strength (s)	1 mg /72 hours
Applicant Name	Perrigo R&D Company
Address	515 Eastern Ave. Allegan, MI 49010
Applicant's Point of Contact	Valerie Gallagher
Contact's Phone Number	(269) 673-8451
Contact's Fax Number	(269) 673-7655
Submission Date(s)	23 February 2007
First Generic	Yes
Reviewer	Svetlana Cherstniakova, Ph.D.
Study Number (s)	AA31201
Study Type (s)	Transdermal Delivery System
Strength (s)	0.15 mg / 0.02 mg /24 hours
Clinical Site	MDS Pharma Services
Clinical Address	2350 Cohen Street Saint-Laurent, Montreal Quebec, H4R 2N6 Canada
Analytical Site	(b) (4)
Analytical Address	

I. EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product. The firm has used dissolution method per DBE recommendation provided in a recent control correspondence (OGD # 05-1125, Perrigo Company). The method uses USP Apparatus 7 (reciprocating disk), with Stroke of 2-3 cm at a rate of 30-60 cycles/minute, 20 mL distilled water as the dissolution medium and sampling times 1, 2, 4, 6, 24, 48, 72 hours. The dissolution testing was conducted on 12 units each of the test and reference products. However, the firm did not submit individual dissolution data of drug release for the test and reference products. The dissolution testing is incomplete pending firm's submission and review of the complete data.

.

The DBE will review the fasting BE study at a later date.

Table 1: SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended 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	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are all eight electronic summary biotables present			☒	☐	☐
Are electronic summary biotables in pdf format			☒	☐	☐

Comments:

The firm performed one BE study on the 1 mg /72 hours Scopolamine Transdermal Patch and measured scopolamine, calculating the 90% CI for the analyte. The BE tables are on the EDR.

*The firm did not submit the individual dissolution data of drug release for the test and reference products.

II. DISSOLUTION DATA

FDA-recommended method (OGD # 05-1125, Perrigo Company):

With respect to the dissolution testing on the Scopolamine Transdermal Therapeutic System, 1 mg/72 hours, the Office of Generic Drugs (OGD) provided the following recommendation to Perrigo through a control correspondence OGD # 05-1125:

- Please develop a method for determining in-vitro release of your product based on the USP 28 Transdermal Delivery Systems-General Drug Release Standards. Please conduct drug release testing on 12 individual dosage units. Sampling time intervals should be selected to characterize drug release from the system in its various performance phases such as start-up of the system to provide assurance against premature release of the drug, steady-state release, and cumulative drug release over the application period. A minimum of six different time points should be used to characterize drug release.

- In addition, please perform the following dissolution test for your product:

Apparatus:	USP Apparatus 7 (reciprocating disk)
	Stroke of 2-3 cm at a rate of 30-60 cycles/minute
Dissolution vessels:	25 x 150 mm test-tubes containing 20 mL media
Media:	Distilled water
Temperature:	32 + 0.3 ºC
Sampling times:	1, 2, 4, 6, 24, 48, 72 hours

Tolerances will be determined upon review of the drug release data.

In supplement's review (SCM-030) to NDA 17-874 dated July 2, 2002, the following specifications* for the percent of scopolamine released with time are recommended for Transderm Scop®(scopolamine) Transdermal Therapeutic System:

Percent of Drug Released	
Sampling Time	Specification
6 hour	(b) (4)%
12 hour	%
24 hour	%
48 hour	%
72 hour	%

*The recommended specifications are based on the mean ± 10% values

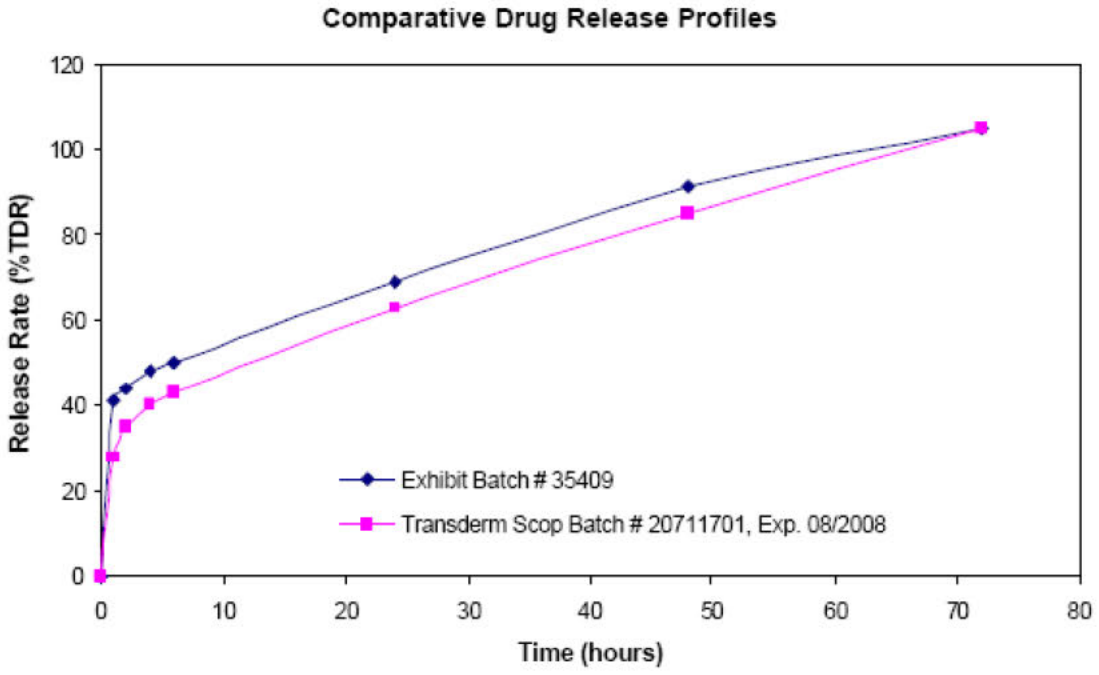
The firm has used dissolution method as recommended by the OGD. The dissolution results are summarized in the Table below.

Table 2: SUMMARY OF IN VITRO DISSOLUTION DATA

Dissolution Conditions	**Apparatus:**	Apparatus 7 (reciprocating disks)
	Speed of Rotation:	(b) (4)
	Medium:	Distilled water
	Volume:	20 mL
	Temperature:	32.0 ± 0.3°C
	Stroke depth:	2 - 3 cm
	Dipping speed:	(b) (4)
Firm's Proposed Specifications	See Below	
Dissolution Testing Site (Name, Address)	Aveva Drug Delivery Systems, (b) (4) 3250 Commerce Parkway, Miramar, FL 33025	

Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times							Study Report Location
				1 hr	2 hrs	4 hrs	6 hrs	24 hrs	48 hrs	72 hrs	
Perrigo Exhibit Batch: Scopolamine Transdermal Therapeutic System Lot # 35409, July 26, 2006	Transdermal Film, Extended Release – 1 mg/72 hr	12	Mean	41	44	48	50	69	91	105	Module 3, 3.2.P.2.2.1.3
			RSD (%)	4.7	2.2	1.9	2.1	3.6	4.2	3.8	
RLD: Transderm Scop® Lot # 20711701, Exp 08/2008	Transdermal Film, Extended Release – 1 mg/72 hr	12	Mean	28	35	40	43	63	85	105	Module 3, 3.2.P.2.2.1.3
			RSD (%)	6.1	3.6	2	1.8	1.6	1.5	1.5	
Firm's Proposed Specifications										(b) (4)	

Comparative Dissolution Profiles



III. COMMENTS

Currently, the OGD Dissolution Data Base does not provide any dissolution method on scopolamine.

The in vitro dissolution method in the original NDA 17-874 for the in vitro release testing of Transderm Scop patches are as follow (see DFS N 017874 SCM 030 C 20-Mar-2002): each patch is removed from its package, and the release liner is discarded from the system. (b) (4)

[redacted]

Samples are collected without filtering at time intervals of 6, 24, 48, and 72 hr and analyzed for scopolamine content by HPLC.

The firm has used dissolution testing on 12 individual dosage units of the test and reference product, and 6 different time points to characterize drug release per the OGD recommendation in the control correspondence (OGD # 05-1125, Perrigo Company). It is noted that the OGD recommended method is very similar to that in the NDA method described above.

However, the firm did not provide the individual data of drug release for the test and reference products. Therefore, the firm is requested to submit the individual dissolution data in order to determine the release specifications for its transdermal system. The dissolution testing is incomplete pending firm's submission of additional dissolution data.

IV. DEFICIENCY COMMENTS

The firm did not provide the individual data of drug release of the test and reference product.

V. RECOMMENDATIONS

1. The dissolution testing conducted by Perrigo Company on the test product, Scopolamine Transdermal Patch, 1 mg /72 hours Lot # 35409, is incomplete due to the reasons given in the deficiency comments.

2. The firm should be notified of the new BE Summary Tables available on the FDA website.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78830

APPLICANT: Perrigo R&D Company

DRUG PRODUCT: Scopolamine Transdermal Patch, 1 mg /72 hours

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The following deficiency has been identified:

1. The dissolution testing is incomplete. Your dissolution results did not include individual data of drug release for the test and reference products. Please submit drug release data for the 12 units of the test and reference products.

2. The Division of Bioequivalence has developed new data summary tables in a concise format consistent with the Common Technical Document (CTD). Please provide complete tables and send them with the rest of the bioequivalence submission. The tables are available in Word and PDF format under the title "Model Bioequivalence Data Summary Tables" in our website at http://www.fda.gov/cder/ogd/index.htm. To improve the efficiency of the Division, these tables should be provided in all pending and future ANDA submissions.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

VI. OUTCOME

ANDA 78830

[NOTE: The fasting study is pending review]

1.	**Dissolution (Dissolution Data)**	Strength:	1 mg /72 hours
	(DIS)	Outcome:	**IC**
	Submission Date(s)	23 February 2007	

BIOEQUIVALENCE OUTCOME DECISIONS:	AC – Acceptable IC – Incomplete UN – Unacceptable WC – Without Credit

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/s/

Svetlana Cherstniakova
9/10/2007 10:06:43 AM
BIOPHARMACEUTICS

Chandra S. Chaurasia
9/10/2007 10:15:41 AM
BIOPHARMACEUTICS

Barbara Davit
9/12/2007 03:46:36 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78830

OTHER REVIEWS

REGULATORY PROJECT MANAGER'S CLINICAL SITE SELECTION REVIEW FOR OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) INSPECTION

ANDA#	078830
Product	Scopolamine Transdermal System, 1 mg/3 days
Sponsor	Perrigo R&D Company 515 Eastern Avenue Allegan, MI 49010
Submission Date	3/14/2014
DCR ANDA Reviewer	Sunny Tse, Ph.D.
Inspection Requestor	Eunjung (Esther) Chuh, Pharm.D. Medical Affairs Coordinator Division of Clinical Review (DCR) Office of Generic Drugs
Date of Review	9/23/2014
Approving Official	Lesley-Anne Furlong, M.D. Director (Acting), Division of Clinical Review Office of Generic Drugs

Following clinical study was submitted to evaluate adhesion.

Study Number and Title	Study No. 11325301 A Study to Evaluate the Relative Adhesive Properties of a Test Scopolamine Transdermal Therapeutic System, 1.31 mg (Manufactured by AVĒVA Drug Delivery Systems, an Apotex Company; Distributed by Perrigo) Compared to TRANSDERM-SCŌP® (Scopolamine) Transdermal Therapeutic System, 1.5 mg (Manufactured by ALZA Corporation; Distributed by Novartis Consumer Health, Inc.) in Healthy Adult Subjects
Study Period	10/21/2013 – 11/17/2013
Total Number of Subjects Enrolled	80
Principal Investigators	**Site No. 01** There was no clinical site designated as Site No. 01 for this study. **Site No. 02** Robert A. Weaver, M.D., CPI Novum Pharmaceutical Research Services 11300 Richmond Avenue Houston, TX 77082

	Site No. 03 Darin B. Brimhall, D.O., FACP, CPI Novum Pharmaceutical Research Services 3760 Pecos McLeod Las Vegas, NV 89121

PRINCIPAL INVESTIGATOR	NO INSPECTION HISTORY	LAST INSPECTION VAI & > 5YR	HAS PRIOR INSPECTION HISTORY	DATA UNACCEPTABLE IN PRIOR INSPECTION
Robert A. Weaver, M.D., CPI	✓		Pending (b) (4) for (b) (4)	
Darin B. Brimhall, D.O., FACP, CPI	✓		Pending (b) (4) for (b) (4) (Also pending (b) (4) for NDA 204242; NDA 205931 on (b) (4) and (b) (4) for ANDA 205256 for PK Study)	

RECOMMENDATION:

Each of the clinical investigators has pending or prior inspectional history (see above) for clinical studies. Therefore a new inspection will not be requested at this time. The investigators Darin B. Brimhall, D.O., FACP, CPI and Robert A. Weaver, M.D., CPI do not have any inspection history on a clinical endpoint study. (b) (4) (b) (4)

Principal Investigator	Number of Subjects
Robert A. Weaver, M.D., CPI Novum Pharmaceutical Research Services 3320 Walnut Bend Lane Houston, TX 77042 United States of America (USA) Darin B. Brimhall, D.O., FACP, CPI Novum Pharmaceutical Research Services 3760 Pecos McLeod Las Vegas, NV 89121 United States of America (USA)	Total 80 enrolled for the Study

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/s/

EUNJUNG E CHUH
09/23/2014

NITIN K PATEL
09/23/2014
ON BEHALF OF LESLEYANNE FURLONG

MEMORANDUM

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

DATE: December 27, 2007

TO: Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs (HFD-600)

FROM: Mark Seaton, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. Martin K. Yau 12/27/07
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering ANDA 78-830,
Scopolamine Extended Release Transdermal Film,
1 mg/72 hr,
Sponsored by Perrigo Pharmaceuticals.

At the request of the Division of Bioequivalence (DBE), Office of Generic Drugs, the Division of Scientific Investigations initiated an audit of the following bioequivalence study:

Protocol number PRG-603: A Multiple Site Study to Evaluate the Cumulative Skin Irritation and Sensitization Potential and Adhesive Properties of a Placebo Scopolamine Transdermal Delivery System (Modified Draize Test)

This was a multi-site, clinical study. DBE requested inspections of the following sites:

Clinical Site 01: (n = 157)	Novum Pharmaceutical Research Services 5900 Penn Avenue Pittsburgh, PA 15206
Clinical Investigator:	Shirley Ann Kennedy, M.D.

Clinical Site 02: (n = 67)	Novum Pharmaceutical Research Services 3320 Walnut Bend Lane Houston, TX 77042
Clinical Investigator:	Soran Hong, M.D.
Clinical Site 03: (n = 72)	Novum Pharmaceutical Research Services 3760 Pecos-McLeod Road Las Vegas, NV 89121
Clinical Investigator:	Daryl G. Ficklin, D.O.

No forms FDA-483 were issued to any of the three sites. No issues were noted that would affect the integrity of the study data.

Conclusion:
Following our evaluation of the inspectional findings, DSI concludes that data from Study PRG-603 is acceptable for the Agency's review.

After you have reviewed this transmittal memo, please append it to the original ANDA submissions.

Mark J. Seaton, Ph.D.

Final Classifications:
Shirley Ann Kennedy, M.D., Novum Pharmaceutical Research Services - NAI
Soran Hong, M.D., Novum Pharmaceutical Research Services - NAI
Daryl G. Ficklin, D.O., Novum Pharmaceutical Research Services - NAI

cc:
HFD-45/RF
HFD-48/Seaton/Himaya/CF
HFD-600/ Catterson/Hixon/ANDA 78-830
Draft: MJS 12/21/07
Edit: MKY 12/21/07
DSI:5789; O:\BIOEQUIV\EIRCOVER\78830per.sco.doc
FACTS: 853364

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/s/

Mark Seaton
12/27/2007 12:54:48 PM
CSO
Hard copy signed by Martin Yau on 12/27/07

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78830

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: A. Potter Team: **Approval Date:** 1/30/2015

☒ **PI** ☐ **PII** ☐ **PIII** ☐ **PIV** (*eligible for 180 day exclusivity* ☐ **Yes** ☒ **No)** ☐ **MOU** ☒ **RX or** ☐ **OTC**

ANDA #: 078830 Applicant: Perrigo R&D Company Established Product Name: Scopolamine Transdermal Therapeutic System, 1 mg/3 days.

Basis of Submission (RLD): Transderm Scop
(Is ANDA based on an approved Suitability Petition? ☐ *Yes* ☒ *No)*

Does the ANDA contain REMS? ☐ **Yes** ☒ **No** *(If YES, initiate approval action 6 weeks prior to target action date)*

Regulatory Project Manager Evaluation: **Date: 1/5/2015**

☒ Date last Complete Response (CR) letter was issued -- Date 5/31/2013

☐ Previously reviewed and tentatively approved (if applicable) --- Date _____

Date of Application 2/23/2007	Original Received Date 2/26/2007	Date Acceptable for Filing 2/26/2007

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 9/22/2014 Date of Acceptable Dissolution 11/9/2014 Date of Acceptable Bioequivalence 11/6/2014 Date of Acceptable Labeling 12/24/2014	If applicable: Date of Acceptable Microbiology N/A Date of Acceptable Clinical Review 1/21/15 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: 3/27/2015	
☒	☐	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 1/29/15	
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 1/26/15	
☐	☐	Paragraph IV Evaluation completed (if applicable), Date N/A	
☒	☐	Quality Endorsement completed, Date 1/28/15	
☒	☐	Bioequivalence Endorsement completed, Date 1/23/15	
☒	☐	Labeling Endorsement completed, Date 1/23/15	
☐	☐	REMS Endorsement (if applicable), Date N/A	
RPM Team Leader Endorsement and Action Package Verification			
☒	☐	RPM Team Leader Endorsement completed, Date 1/29/15	
Final Decision and Letter Sign-off			
☒	☐	Final Decision recommending approval/tentative approval completed, Date 1/30/2015	
☒	☐	Approval/Tentative Approval letter electronically signed, Date: 1/30/2015	
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	

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

This page to be completed by the RPM

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 1/23/2015
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: Is applicant eligible for 180 day 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 = Transderm Scop (NDA 17874) Application submission 2/26/2007 with a PI certification as there were no patents or exclusivities associated with the RLD at the time of filing. Acknowledgment letter signed 5/24/2007.
There have been no patents or exclusivities added to the NDA in the OB since the original ANDA submission. There are no legal barriers to approval of the application and it is eligible for immediate Full Approval.

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

8. Final Decision

Date: 1/30/2015
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 = Transderm Scop (NDA 17874). The applicant provided a PI certification. There are no patents or exclusivities associated with the RLD. There are no legal barriers to approval of the application. Chemistry acceptable 9/22/2014. Bio acceptable fasting BE study, dissolution 1/16/2009, skin irritation, sensitization and adhesion studies acceptable 1/15/2015. Labeling acceptable 12/23/2014, TL sign-off 1/25/2015. EES acceptable till 3/27/2015. This is a 1st generic and ready for immediate Full Approval.

EES DATA:

(b) (4)

Application History:

Click here to enter text.

APPEARS THIS WAY ON ORIGINAL

Orange Book Report:

Click here to enter text.

APPEARS THIS WAY ON ORIGINAL

REFERENCES / ASSOCIATED DOCUMENTS

4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Version	Effective date	Name	Role	Summary of changes
01	10/1/2014	Heather Strandberg	Author	New Form

EASILY CORRECTABLE DEFICIENCY EMAIL

ANDA 78830

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Perrigo R&D Company TEL: (2690 673-8451

ATTN: James Chambers FAX: (269) 673-7655

FROM: Surjit Basi FDA CONTACT PHONE: (240) 402-8892

Dear Sir:

This communication is in reference to your abbreviated new drug application (ANDA) dated February 23, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Scopolamine Transdermal System, 1 mg/3 days.

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 within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
CHEMISTRY

If you do not submit a complete response within ten (10) U.S. 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.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Regulatory Project Manager immediately so a complete response may be issued if appropriate.

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.

If you have questions regarding these deficiencies please contact the Regulatory Project Manager, Surjit Basi at (240) 402-8892.

We have completed our review, as amended, and have the following comments:

PRODUCT QUALITY

Drug Substance:

1. (b) (4)

Drug Product:

2. (b) (4)
3.
4.
5.
6.
7.
8.

Sincerely yours,

{See appended electronic signature page}

Bhagwant Rege, Ph.D.
Supervisor, Chemistry V
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

DHAVAL GAGLANI
08/05/2014

OFFICE OF GENERIC DRUGS EXPEDITED REVIEW REQUESTED

ANDA#/SUPPLEMENT#: 78830 APPLICANT: Perrigo R&D Company
DRUG: Scopolamine Transdermal Therapeutic System, 1 mg/3 days DATE OF SUBMISSION:

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 & GDUFA). 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.

4. ☐ **GDUFA.** Year one and year two cohort PIV 180-day eligibility (First Generic)

RECOMMENDATIONS:

DISCIPLINE	STATUS	SIGNATURE/DATE
Team Project Manager (PM must Endorse)	Grant☒ Deny☐	SKB/June 30, 2014
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☐	RLW/June 30, 2014

RETURN TO PROJECT MANAGER CHEMISTRY TEAM:

ENTER FORM INTO DAARTS DATE June 30, 2014

Paste Email Copy Below:
Surjit:

Yes, for consistency. Perrigo's ANDA meets the current criteria – no listed patents in the Orange Book and no approved generics.

Thank you,

Bob

From: Basi, Surjit
Sent: Tuesday, June 24, 2014 12:07 PM
To: West, Robert L
Subject: RE: ANDA 78830 Expedited Review Request

Hi Bob,

I just wanted to confirm that this ANDA will not be accepted for expedited review.

Thank you,
Surjit

From: Basi, Surjit
Sent: Wednesday, June 18, 2014 4:09 PM
To: West, Robert L
Subject: RE: ANDA 78830 Expedited Review Request

Hi Bob,

It does look like this ANDA has had some history. We have sent them 4 minor CMC deficiency letters, with the latest one being a Complete Response sent on 5/31/13. They responded to the minor CR on 3/14/14. Clinical is to start its second round of review (first round found deficiencies related to adhesion), EES is pending, and labeling was already found inadequate. CMC and Clinical have not yet picked up the review for this ANDA, and I wanted to make sure I prioritized their reviews appropriately.

Not sure how strong of a candidate this is for expedited review based on its history.

Thanks,
Surjit

From: West, Robert L
Sent: Wednesday, June 18, 2014 2:35 PM
To: Basi, Surjit
Subject: RE: ANDA 78830 Expedited Review Request

With an ANDA number like 78-830, that ANDA has been around a long time. Is it a viable application? Are there major issues holding it up? I'm not in favor of expending our resources on it if there are.

Thanks,

Bob

From: Basi, Surjit
Sent: Wednesday, June 18, 2014 2:06 PM
To: West, Robert L
Subject: ANDA 78830 Expedited Review Request

Hi Bob,

ANDA 78830/Perrigo, (b) (4) for Scopolamine TDS and designated as first generic with no blocking patents or exclusivities. (b) (4)

ANDA 78830/Perrigo has not been granted expedited, as the firm has not requested for it.

Should we grant ANDA 78830/Perrigo expedited review based on MaPP 5240.3 (b) (4) (b) (4)

Regards,
Surjit

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

/s/

SURJIT K BASI
06/30/2014

ROBERT L WEST
07/01/2014
Deputy Director, Office of Generic Drugs

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 78830

Perrigo R & D Company
Attention: James Chambers
Manager, Regulatory Affairs
515 Eastern Ave
Allegan, MI 49010

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated February 23, 2007, received February 26, 2007, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Scopolamine Transdermal Therapeutic System,1 mg /3 days.

We also refer to the teleconference between representatives of your firm and the FDA on July 17, 2013. The purpose of the requested teleconference was to discuss deficiencies noted in the Complete Response Letter dated May 31, 2013.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Esther Chuh, Regulatory Project Manager, at (240) 276-8530.

Sincerely,

{See appended electronic signature page}

Eunjung Esther Chuh, Pharm.D.
Regulatory Project Manager
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: [Post CR]

Meeting Date and Time: [July 17, 2013, 12:30 PM to 1:00 PM]

Application Number: [078830]
Product Name: [Scopolamine Transdermal Therapeutic System]
Sponsor/Applicant Name: [Perrigo R&D Company]

Meeting Recorder: [Nitin Patel and Tania Mazza]

FDA ATTENDEES

Clinical

John R. Peters, MD, Division Director
Stella C. Grosser, PhD, Statistical Team Leader
Huaixiang (Helen) Li, PhD, Statistical Reviewer
Sarah H. Seung, PharmD, Clinical Reviewer
Nitin K. Patel, PharmD, Medical Affairs Coordinator

Quality
Andre Raw, Ph.D., Division Director, Chemistry 1
Bhagwant Rege, Ph.D., Team Leader, Team 12
Shanaz Read, Ph.D., Chemistry reviewer
Tania Mazza, Pharm.D., Product Quality regulatory Project Manager

SPONSOR ATTENDEES

Richard Stec – Vice President, Global Regulatory Affairs
Valerie Gallagher – Director, Regulatory Affairs
James Chambers –Senior Manager, Regulatory Affairs
Vamshidhar Pillarishetty – Regulatory Affairs Project Manager
Beatriz North – Senior Director, Clinical Affair
Jonathan Schwartz – Manager, Clinical Affairs
Chris Adams – R&D, Aveva
Mushtaq Fruitwala – Sr. Director, Strategic Development

1.0 BACKGROUND

(i) Purpose of meeting: To discuss the questions submitted by Perrigo on June 14, 2013, based on the Complete Response Letter issued to Perrigo on May 31, 2013.

(ii) Names of drug: Scopolamine Transdermal Therapeutic System, 1 mg/3 days

(iii)Expected outcome for the meeting - To provide response to Perrigo's questions submitted on June 3, 2013.

2. DISCUSSION

2.1. Category/Clinical

Question 1:

Please clarify why a lower-bound statistical methodology of analyzing adhesion as outlined in section 10.4 of protocol PRG-604 does not meet acceptability criteria for demonstrating non- inferiority.

The protocol specified statistical analysis method states: "Non-inferiority of the test product relative to the reference product will be assessed with respect to % adhesion by the lower bound of a one-sided 95% confidence interval on the ratio of the geometric means by constructing first on the log scale a confidence internal on the difference of the least squares (LS) means, and then transforming the endpoints by anti-logarithm back to the original scale. Non-inferiority will be based on whether the lower limits of the confidence interval for the ratio of geometric means (expressed in %) is greater than 80%."

Perrigo's adhesion study results demonstrated that the ratio of least squares means of the Test product patch over the reference product patch for the percent adhesion was 97% with a lower 95% confidence interval limit of 91%, well within the protocol specified criteria of >80%. Perrigo believes this methodology provides sufficient data to demonstrate non-inferiority of Test Product to the Reference Product.

FDA Response to Question 1:

DCR would like to clarify that we reviewed your adhesion study using the upper-bound statistical methodology of analyzing adhesion data as recommended in the current FDA bioequivalence guidance on scopolamine transdermal system. This teleconference is for clarification purposes only, and we are unable to consider or discuss the acceptance of your statistical methodology at this meeting. We recommend that you submit a request for a formal meeting, in which we would be able to include the appropriate experts. In such a forum discussion of acceptable scientific support for any new statistical or study methodology could occur. Such data may suggest that a change in FDA guidance recommendations might be appropriate.

Discussion:

Perrigo presented their opinion that neither statistical methodology, Perrigo's nor FDA's, is superior to the other, and discussed that there are two common themes that challenge us:

(1) Lack of a clinical relevant definition of the difference in mean adhesion scores.
(2) Scoring mechanism – since there is a minimum value of 0, for products that adhere well, any slight difference in the cumulative partial adhesion score is going to make a wide statistical swing in either direction for the test or reference product.

Perrigo feels that the data provided is adequate to demonstrate non-inferiority along a lower bound confidence interval, and requested to hear more on the Agency's thinking that either challenges that, or supports using the upper-bound confidence interval.

DCR clarified that Perrigo's adhesion study data were reviewed using the current statistical analysis methodology provided in current FDA guidance, which is based around an upper-bound confidence interval, on an absolute scale rather than a log transformed scale. DCR stated that the statistical guidance on adhesion was put together after considerable thought and evaluation of what would be the best methodology, and agreed with Perrigo that for products that have very good adhesion profiles, small changes can lead to large swings in terms of the result. However, as stated by Perrigo "…neither statistical methodology, Perrigo's nor FDA's, is superior to the other". Therefore, if the Perrigo method and the FDA method are not producing the same results, then we would need to re-assess both of these methodologies. DCR stated that the purpose of this teleconference is for clarification of the clinical comment that was conveyed, and not to negotiate whether we can accept Perrigo's methodology.

Perrigo was interested in having a discussion about clinical relevance and meaningful degrees of patch detachment, and pointed out, that from observing the raw data from the Perrigo study, it is very clear that the cumulative adhesion on a percent basis, at each time point is comparable if not very much similar to the reference product, as well as the fact that during the seventy-two hour period, the reference product had detachment of one patch, whereas the Perrigo test product had none.

DCR stated that unlike the Office of New Drugs, the Office of Generic Drugs cannot use clinical judgment to make a regulatory approval decision when comparing a proposed generic product to a reference product. DCR posited that consistent decision making based on published guidance, specific methodology, and statistical evidence is necessary.
DCR understood that Perrigo is proposing that their methodology comes to a different result and would like the FDA to accept that methodology. DCR stated that they can certainly consider that, however, it would have to be at a different kind of meeting with FDA experts who would be better able to consider the options and make appropriate recommendations. .

Perrigo inquired if FDA would be amenable to using a different scoring method using a dichotomous endpoint (of 0 and/or 1 being considered as a success) and for Perrigo to submit that data for evaluation.

DCR stated again, that this would require a much more focused discussion and DCR alone would not be able set FDA policy in today's clarification meeting. DCR is certainly interested in pursuing this bigger discussion and is in agreement with Perrigo, that the methodology as it stands could bear another look because over time products have become much better than when some of these decisions were made. DCR stated that this is not something that we can do in this teleconference, and additionally, DCR cannot promise that the kind of evaluation Perrigo is suggesting would lead to an approval, even if Perrigo was able to provide favorable data, because it would be a policy decision.

Perrigo inquired if FDA would be amenable to having a discussion and sharing information about how the methodology that was issued in the guidance was developed, and why that methodology would be more appropriate.

DCR agreed that they would be amenable to having that discussion at a Type C meeting.
At a Type C meeting, Perrigo will need to do the full preparation of providing their proposal(s) through pre-meeting materials. It will also enable DCR to gather appropriate experts from within OGD and CDER, who can discuss the issues and then make some decisions.

Perrigo conveyed that the comments from this meeting were most helpful in deciding how to move forward.

DCR thanked Perrigo for bringing forward some interesting questions and having some good suggestions. DCR also emphasized that they are anxious and willing to work with Perrigo at a Type C meeting.

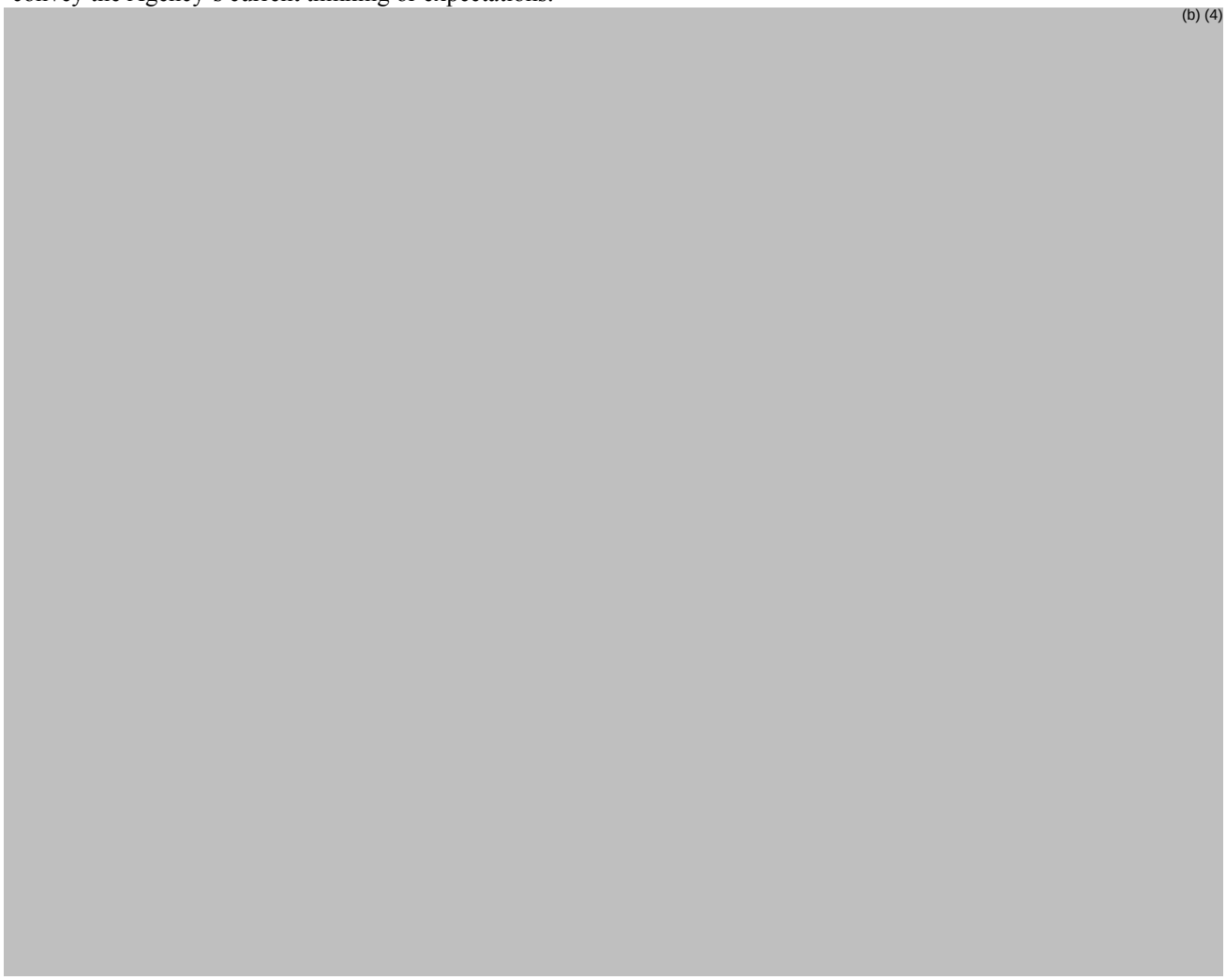
2.2. Category/Quality

Perrigo's request:

FDA Comment# 2 in CR letter: The Agency requires evidence that the formulation of a generic product is not less safe than the RLD. We acknowledge that it is possible that different transdermal formulations of the same drug may have different responses to "in-use conditions". To ensure that the RLD labeling with respect to swimming/showering is applicable to the ANDA product, please provide information about the formulation performance to ensure that the sensitivity to in-use conditions like water/hot water exposure of the generic product is not more pronounced than that of the RLD. You may design and provide an in vitro study (e.g., skin flux permeation study with "stressed" conditions to mimic certain in use conditions) to compare in vitro release data to the RLD at normal and "stress" situations: If the generic product was not more sensitive than the RLD, it would be acceptable. Such in vitro data would assure that the proposed generic TDDS product would not create a greater risk when exposed to in-use conditions than the RLD.
Please refer to the FDA response to the CP 2012-P-0932 (see link below) for additional information.
http://ww-w.regulations.gov/#!documentDetail;D=FDA-2012-P-0932-0003
As a result of the Agency's request to provide evidence of the sensitivity to certain in-use conditions, Perrigo has reviewed the referenced CP 2012-P-0932, and agrees to conduct an in vitro study. Our aim is to provide all data necessary to achieve review of the amendment in a single cycle.

Perrigo's Request for Clarification:
Before commencing such a study, Perrigo seeks clarification regarding methodology, conditions, and comparative evaluation criteria for the requested in-vitro study which is intended to "mimic certain in-use conditions" as there do not appear to be FDA, ICH, or other industry standards for this type of study publically available for reference that convey the Agency's current thinking or expectations.

(b) (4)



(b) (4)

Data evaluation:

1-Point to point non-inferiority comparison is recommended, i.e. cumulative score will not provide an adequate assessment of the patch performance over the 3-day use period

2-f2 comparison is not recommended

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

None

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/s/

EUNJUNG E CHUH
09/27/2013

QUALITY DEFICIENCY - MINOR

ANDA 078830

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: Perrigo R & D Company

TEL: 269-686-1729

ATTN: Diane L. Morgan

FAX: 269-673-7655

FROM: Frank J. Nice

FDA CONTACT PHONE: (240) 276-8555

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated February 23, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Scopolamine Transdermal Therapeutic System, 1 mg/72 hrs.

Reference is also made to your amendments dated April 16 and April 17, 2012.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents 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/

ANDA: 078830

APPLICANT: Perrigo Company

DRUG PRODUCT: Scopolamine Transdermal Therapeutic System, 1 mg/72 h.

A. The deficiencies presented below represent MINOR deficiencies.

(b) (4)

1.

2.

3.

4.

5.

6.

7.

B. Please note and acknowledge the following:

1. 

2.

Sincerely yours,

{See appended electronic signature page}

Glen J. Smith
Director
Division of Chemistry 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/

BINGYUAN WU
07/11/2012
Acting for Susan Rosencrance

Labeling Comments

ANDA 078830

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773 (240-276-8988)

TO: Perrigo R&D Company

TEL: 269-673-8451

ATTN: Valerie Gallagher

FAX: 269-673-7655

FROM: Theresa Liu

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 for Scopolamine Transdermal Therapeutic System, 1 mg/3 days.

Pages (including cover and signature page): 4

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

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/

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

ANDA Number: 078830

Date of Submission: February 23, 2007 (Original)

Applicant's Name: Perrigo R&D Company

Established Name: Scopolamine Transdermal Therapeutic System, 1 mg/3 days

---

Labeling Deficiencies:

1. GENERAL – You currently list the total content as 1.3 mg. This differs from the reference listed drug's total content of 1.5 mg. To avoid confusion, we suggest relocating "1.3 mg" to the side panel, and replace it with "1 mg/3 days" as your product strength expression.

2. CARTON, CONTAINER/POUCH –
    a. Please see comment 1.
    b. Please delete trailing zeroes (i.e., "1 mg over 3 days" rather than "1.0 mg over 3 days").

3. INSERT
    a. The way you submitted your PDF file of physician insert is incomplete with the top and bottom cut off. Please resubmit the complete insert labeling.
    b. Please replace all "this product" with "Scopolamine transdermal therapeutic system" throughout your insert text.
    c. DESCRIPTION, second paragraph: "…(3)…delivery of scopolamine from…" [missing 'scopolamine'].

Revise your labeling, as instructed above, and submit final printed labeling electronically. In addition, please provide the labeling in the Structured Product Labeling (SPL) format. http://www.fda.gov/oc/datacouncil/spl.html

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. 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

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug's labeling with all differences annotated and explained.

{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

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/s/

KOUNG U LEE
01/31/2011
For Wm. Peter Rickman

BIOEQUIVALENCY AMENDMENT

ANDA 78-830

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Perrigo R & D Company TEL: 269-686-1729

ATTN: Diane L. Morgan FAX: 269-673-7655

FROM: Nam Chun FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on February 23, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Scopolamine Transdermal Therapeutic System, 1 mg/72 hrs.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **one** 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**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and 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 both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCY

ANDA: 78-830

APPLICANT: Perrigo Pharmaceuticals

DRUG PRODUCT: Scopolamine Transdermal System, 1 mg/72 hr

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

We acknowledge that you have submitted additional dissolution data using the FDA-recommended dissolution method. However, your dissolution testing is still **incomplete**. Please submit comparative *in vitro* dissolution testing on 12 dosage units of the test and reference products in at least three different pH media (i.e., pH 1.2, 4.5 and 6.8 buffers). Agitation speed may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please conduct dissolution testing until at least 80% of the labeled amount of the drug is released. Also, if possible, the dissolution testing should be conducted on your biostudy lots of the test and reference products.

Please submit the comparative dissolution results which should include the individual dosage unit data as well as the mean, range, %CV at each time point for the 12 dosage units tested, and dates of dissolution testing. In addition, please submit the dissolution testing data summary table (Table 5) with the above data. More information on the electronic Common Technical Document (eCTD) format for BE summary tables are provided on http://www. fda.gov/cder/ogd/DBE_tables.pdf.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
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/

Dale Conner

6/30/2008 10:00:46 AM

MINOR AMENDMENT

ANDA 78-830

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Perrigo R & D Company TEL: 269-673-8451

ATTN: Valerie Gallagher FAX: 269-673-7655

FROM: Theresa Liu PROJECT MANAGER: (240) 276-8555

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated February 23, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Scopolamine Transdermal Therapeutic System, 1 mg/72 hrs.

Reference is also made to your amendment dated January 4, 2008.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__**2**__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

II. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-830 APPLICANT: Perrigo Company

DRUG PRODUCT: Scopolamine Transdermal Therapeutic System, 1 mg/72 h.

A. The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)

2.

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry 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/

Damaris Maldonado

4/8/2008 11:33:43 AM

BIOEQUIVALENCY AMENDMENT

ANDA 78-830

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Perrigo R & D Company TEL: 269-686-1729

ATTN: Diane L. Morgan FAX: 269-673-7655

FROM: Keri Suh PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on February 23, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Scopolamine Transdermal Therapeutic System, 1 mg/72 hrs.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **one** 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**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and 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 both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

In an effort to improve document flow and availability to review staff, please submit your response in electronic PDF format, with a signed cover letter and 356h form.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78830

APPLICANT: Perrigo Pharmaceuticals

DRUG PRODUCT: Scopolamine Transdermal System, 1 mg/72 hr

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

Your dissolution data as submitted using the following FDA-recommended dissolution method are acceptable:

The dissolution testing should be conducted in 25 x 150 mm test tubes containing 20 mL of distilled water at 32°C ± 0.3°C using USP apparatus 7 (reciprocating disk) at a stroke of 2-3 cm at a rate of 30-60 cycles/minute.

However, based on the data submitted, your proposed dissolution specifications are not acceptable. Please acknowledge your acceptance of the following DBE-recommended dissolution specifications:

6 hr: (b) (4) %
24 hr: (b) (4) %
48 hr: (b) (4) %
72 hr: (b) (4) %

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
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 Davit
11/30/2007 06:36:50 PM
Signing for Dale P Conner

MINOR AMENDMENT

ANDA 78-830

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Perrigo R & D Company TEL: 269-673-8451

ATTN: Valerie Gallagher FAX: 269-673-7655

FROM: Theresa Liu PROJECT MANAGER: (301) 827-5791

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated February 23, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Scopolamine Transdermal Therapeutic System, 1 mg/72 hrs.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__3__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

In an effort to improve document flow and availability to review staff, please submit your response in electronic PDF format, with a signed cover letter and 356h form.

II. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-830 APPLICANT: Perrigo Company

DRUG PRODUCT: Scopolamine Transdermal Therapeutic System, 1 mg/72 h.

A. The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.
9.
10
11
12
13

B. Comments:

1. The labeling and bioequivalence portions of your application are under review. Deficiencies, if any, will be conveyed to you under separate cover.

2. Please provide updated stability data for the exhibit batch.

3. Please provide representative samples of your product and the RLD to assist in our evaluation of the ANDA. The samples should be sent separately to:

   Theresa Liu, Project Manager, Team 7
   Division of Chemistry II
   Office of Generic Drugs
   7500 Standish Place
   Rockville, MD 20855

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry 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/

Michael S Furness
9/28/2007 10:28:46 AM

BIOEQUIVALENCY AMENDMENT

ANDA 78-830

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Perrigo R & D Company TEL: 269-673-8451

ATTN: Valerie Gallagher FAX: 269-673-7655

FROM: Steven Mazzella PROJECT MANAGER: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on February 23, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Scopolamine Transdermal Therapeutic System, 1 mg/72 hrs.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **1** pages. 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**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and 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 both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

In an effort to improve document flow and availability to review staff, please submit your response in electronic PDF format, with a signed cover letter and 356h form.

ANDA: 78-830

APPLICANT: Perrigo R&D Company

DRUG PRODUCT: Scopolamine Transdermal Patch, 1 mg /72 hours

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission acknowledged on the cover sheet. The following deficiency has been identified:

1. The dissolution testing is incomplete. Your dissolution results did not include individual data of drug release for the test and reference products. Please submit drug release data for the 12 units of the test and reference products.

2. The Division of Bioequivalence has developed new data summary tables in a concise format consistent with the Common Technical Document (CTD). Please provide complete tables and send them with the rest of the bioequivalence submission. The tables are available in Word and PDF format under the title "Model Bioequivalence Data Summary Tables" in our website at http://www.fda.gov/cder/ogd/index.htm. To improve the efficiency of the Division, these tables should be provided in all pending and future ANDA submissions.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Barbara Davit
9/13/2007 06:07:44 PM
Signing for Dale P Conner

MEMORANDUM
Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: June 19, 2007

TO: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence, Division of Scientific Investigations
MPNI, HFD-48

THROUGH: Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs
MPNI, HFD-600

FROM: Debra M. Catterson, R.Ph.
Project Manager, Clinical Review Team
Office of Generic Drugs
MPNI, HFD-600

SUBJECT: Compliance Program 7348.001 – In Vivo Bioequivalence

REQUEST FOR INSPECTION

REFERENCES:

ANDA#	78-830
Product	Scopolamine Extended Release Transdermal Film, 1 mg/72 hr
Sponsor: full address Phone fax	Perrigo Pharmaceuticals 1700 Bathgate Avenue Bronx, NY 10457 (b) (6) 718-960-0167
Sponsor Contact Phone Fax	Beatriz North, MPH, CCRA, Director, Clinical Affairs Perrigo New York 1701 Bathgate Avenue Bronx, NY 10457 (b) (6) 718-960-0167
Submission Date	February 23, 2007

PRIORITY: C

A (highest) = ready for approval in the office
B = ready for approval, clinical study under review
C = pending clinical review

DUE DATE: September 19, 2007

REASON FOR REQUEST:

	Not inspected in the last three years
	For Cause/Violative History
X	New Sites
	Other

Clinical Endpoint Study

TITLE:	A Multiple Site Study to Evaluate the Cumulative Skin Irritation and Sensitization Potential and Adhesive Properties of a Placebo Scopolamine Transdermal Delivery System (Modified Draize Test)
PROTOCOL #:	PRG-603
NUMBER OF STUDY SITES:	3
CRO/SMO:	Marie Mayer, Director, Quality Assurance Novum Pharmaceutical Research Services 5900 Penn Avenue Pittsburgh, PA 15206 Phone: 412-363-3300 Fax: 412-362-5783

SITES TO BE INSPECTED	
Site # 1	Novum Pharmaceutical Research Services (Site 01)
Address	5900 Penn Avenue Pittsburgh, PA 15206
Phone	Tel: 412-363-3300 Fax: 412-362-5783
Investigator (Name/Contact Info)	Shirley Ann Kennedy, M.D.
# of subjects	157
Site # 2	Novum Pharmaceutical Research Services (Site 02)
Address	3320 Walnut Bend Lane Houston, TX 77042
Phone	Tel: 832-251-8100 Fax: 832-251-7133
Investigator (Name/Contact Info)	Soran Hong, M.D.
# of subjects	67
Site # 3	Novum Pharmaceutical Research Services (Site 03)
Address	3760 Pecos-McLeod Road Las Vegas, NV 89121
Phone	Tel: 702-435-3739 Fax: 702-435-7249
Investigator (Name/Contact Info)	Daryl G. Ficklin, D.O.
# of subjects	72

COMMENTS/ADDITIONAL INFORMATION FOR INSPECTORS:

This ANDA is located in the Electronic Document Room (EDR).

CLINICAL STUDY STATUS:

	Study under review
	Study review completed
	Decision:
X	Other: Review not started.

CLINICAL REVIEWER/CONTACT INFORMATION: Not yet assigned to a clinical reviewer.

CC:

HFD-48 (Viswanathan)
HFD-600 (Debra Catterson)
HFD-630 (ANDA# 78-830)

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

/s/

Dena Hixon

6/19/2007 12:51:47 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-830

Perrigo R & D Company
Attention: Valerie Gallagher
515 Eastern Avenue
Allegan, MI 49010

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated May 11, 2007 and your correspondence dated May 15, 2007.

NAME OF DRUG: Scopolamine Extended-release
Transdermal Film, 1 mg/72 hour

DATE OF APPLICATION: February 23, 2007

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 26, 2007

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Theresa Liu
Project Manager
301-827-5791

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 Shimer
5/24/2007 10:43:47 AM
Signing for Wm Peter Rickman

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.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**
*** **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/ ***

ANDA #: 78-830 **FIRM NAME**: PERRIGO R&D COMPANY

PIV: NO **Electronic or Paper Submission:** ELECTRONIC (ECTD FORMAT)

RELATED APPLICATION(S): NA

First Generic Product Received? YES

(PER MARTY 3/26/07)

Bio Assignments:		**Micro Review (No)**
☒ **BPH**	☒ **BCE**	☐
☐ **BST**	☐ **BDI**	

DRUG NAME: SCOPOLAMINE TRANSDERMAL EXTENDED RELEASE

DOSAGE FORM: FILM, 1 MG/72 HR

Random Queue: 7

Chem Team Leader: M. Scott Furness PM: TBD Labeling Reviewer: Koung Lee

Letter Date: FEBRUARY 23, 2007 **Received Date**: FEBRUARY 26, 2007

Comments: EC- 1 YES **On Cards:** YES

Therapeutic Code: 2010400 ANTI-EMETICS

Archival copy: PAPER (ECTD FORMAT) **Sections** I

Review copy: NO E-Media Disposition: YES SENT TO EDR

Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product

(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Iain Margand **Date 5/17/07**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: _____	**Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

5/11/07See Bio and Clinical Team First Generic Reviews in DFS. During the T-con, I conveyed the Clinical Teams comments to Diane Morgan regarding skin sensitization studies. I informed Diane this information would be required as part of the Bio review. Since this information will be required for review, the gathering of the information now would help expedite the review process.
Requested a Debarment and List of Convictions Statement with original signature.
Requested an Exclusivity Statement.
Requested a Contact person for the API manufacturer.
Requested a Batch formulation for the drug product largest intended batch.
Requested a Technical drawing for the drug product container.

5/15/07: Requested information sent via fax.

Contact: Diane Morgan 269-686-1729

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2** **Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: FEBRUARY 23, 2007	☒
*	**Table of Contents (paper submission only)** N/A	☐
1.3.2	**Field Copy Certification (original signature)** N/A **(N/A for E-Submissions)**	☐
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) Y see amendment 2. List of Convictions statement (original signature) Y	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455) YES	☒
1.3.5	**1.3.5.1** **Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations N **1.3.5.2** **Patent Certification** 1. Patent number(s) N/A 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☒ PII ☐ PIII ☐ PIV ☐ No Relevant Patents ☐ 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YE no exclusivities (see amendment)	☒

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 Y b. Type III DMF authorization letter(s) for container closure Y 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A	☒
1.12.11	**Basis for Submission** NDA# : 17-874 Ref Listed Drug: TRANSDERM SCOP Firm: NOVARTIS CONSUMER HEALTH, INC. ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same 2. Active ingredients Scopolamine 3. Inactive ingredients N/A 4. Route of administration Transdermal 5. Dosage Form Topical patch 6. Strength 1 mg/72 hr	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): Electronic, N/A	☐
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) Y **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained Y **1.14.1.3** 1 package insert (content of labeling) submitted electronically Y ***Was a proprietary name request submitted? No (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained Y **1.14.3.3** 1 RLD label and 1 RLD container label Y	☒

ACCEPTABLE

2.3	**Quality Overall Summary** **E-Submission: X____PDF (archive) ____ Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **Question based Review (QbR) X___ YES _____ NO** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** **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** **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** **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**	☒

2.7	**Clinical Summary (Bioequivalence)** **E-Submission: X___PDF (archive) ____ Word Processed e.g., MS Word** **2.7.1** **Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1** **Background and Overview** **2.7.1.2** **Summary of Results of Individual Studies** **2.7.1.3** **Comparison and Analyses of Results Across Studies** 1. Summary Bioequivalence tables: Table 1. Summary of Comparative Bioavailability (BA) Studies Table 2. Statistical Summary of the Comparative BA Data Table 4. Summary of In Vitro Dissolution Studies **2.7.1.4** **Appendix**	☒

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1** **Nomenclature** **3.2.S.1.2** **Structure** **3.2.S.1.3** **General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers Y 2. Manufacturing Responsibilities Y 3. Type II DMF number for API DMF # (b) (4) 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization**	☒

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) Y **3.2.S.4.2** **Analytical Procedures** Y **3.2.S.4.3** **Validation of Analytical Procedures** Y **1.** Spectra and chromatograms for reference standards and test samples Y 2. Samples-Statement of Availability and Identification of: a. Drug Substance Y b. Same lot number(s) Y **3.2.S.4.4** **Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) Y 2. Applicant certificate of analysis Y **3.2.S.4.5** **Justification of Specification** Y	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems**	☒
3.2.S.7	**Stability**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition Y 2) Inactive ingredients are appropriate per IIG, COMIS and Control Correspondence - see attached	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report	☒
3.2.P.3	**Manufacture** **3.2.P.3.1** **Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) YES 2. CGMP Certification: YES 3. Function or Responsibility YES no testing of API or Drug Product 4. CFN or FEI numbers **3.2.P.3.2** **Batch Formula** Batch Formulation see amendment **3.2.P.3.3** **Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified (b) (4) 3. If sterile product: Aseptic fill / Terminal sterilization N/A 4. Reprocessing Statement Y **3.2.P.3.4** **Controls of Critical Steps and Intermediates** Y **3.2.P.3.5** **Process Validation and/or Evaluation** N/A 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill)	☒
3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified see sec. 3.2.R.1.P.2.2 **3.2.P.4.1** **Specifications** 1. Testing specifications (including identification and characterization) Y 2. Suppliers' COA (specifications and test results) Y **3.2.P.4.2** **Analytical Procedures** Y **3.2.P.4.3** **Validation of Analytical Procedures** Y **3.2.P.4.4** **Justification of Specifications** Applicant COA Y	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1** **Specification(s)** Y **3.2.P.5.2** **Analytical Procedures** Y **3.2.P.5.3** **Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form Y 2. Same lot numbers Y **3.2.P.5.4** **Batch Analysis** Certificate of Analysis for Finished Dosage Form Y lot # 35409 **3.2.P.5.5** **Characterization of Impurities** Y **3.2.P.5.6** **Justification of Specifications** Y	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) Y 2. Components Specification and Test Data Y 3. Packaging Configuration and Sizes Y 4. Container/Closure Testing Y 5. Source of supply and suppliers address see 3.2R.1.P.2.3	☒
3.2.P.8	**3.2.P.8.1** **Stability (Finished Dosage Form)** 1. Stability Protocol submitted Y 2. Expiration Dating Period (b) (4) **3.2.P.8.2** **Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments Y **3.2.P.8.3** **Stability Data** 1. 3 month accelerated stability data Y 2. Batch numbers on stability records the same as the test batch 35409	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

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) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

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 see attached Theoretical Yield Actual Yield Packaged Yield **3.2.R.1.P.2** **Information on Components** Y **3.2.R.2.P** **Comparability Protocols** N/A **3.2.R.3.P** **Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

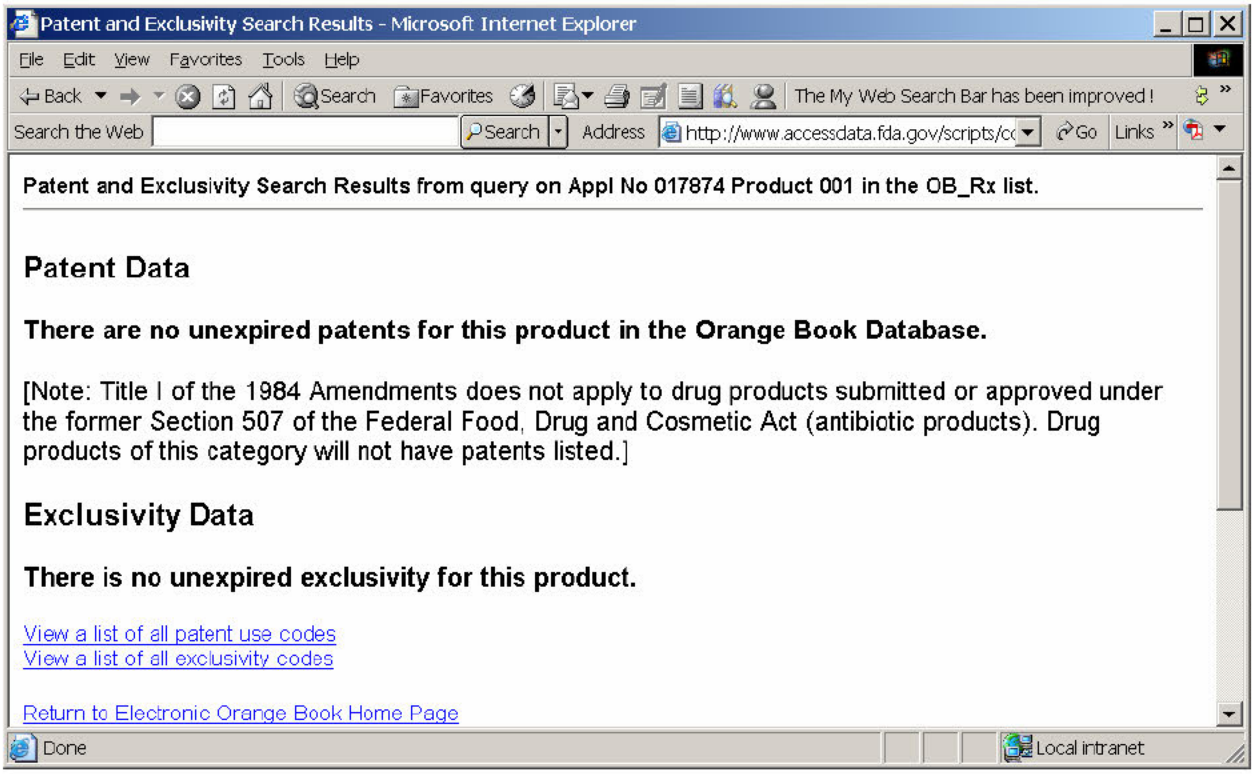
MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☒
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) N/A b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) N/A **2. Lot Numbers of Products used in BE Study(ies):** 35409 **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☒
	5.3.1.2 **Comparative BA/BE Study Reports** 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. Summary Bioequivalence tables: Table 6. Demographic Profile of Subjects Completing the Comparative BA Study Table 7. Incidence of Adverse Events in Individual Studies Table 8. Reanalysis of Study Samples **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 4. Summary of In Vitro Dissolution Studies Table 5. Formulation Data **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 3. Bioanalytical Method Validation **5.3.7** **Case Report Forms and Individual Patient Listing**	☒

5.4	**Literature References**	X
	Possible Study Types:	
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) NA 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) see attached 2. EDR Email: Data Files Submitted: NA 3. In-Vitro Dissolution: NO	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 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). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% or 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** YES 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) see attached 2. In-Vitro Dissolution YES 3. EDR Email: Data Files Submitted YES SENT TO EDR 2. Adhesion Study YES 3. Skin Irritation/Sensitization Study YES	☐



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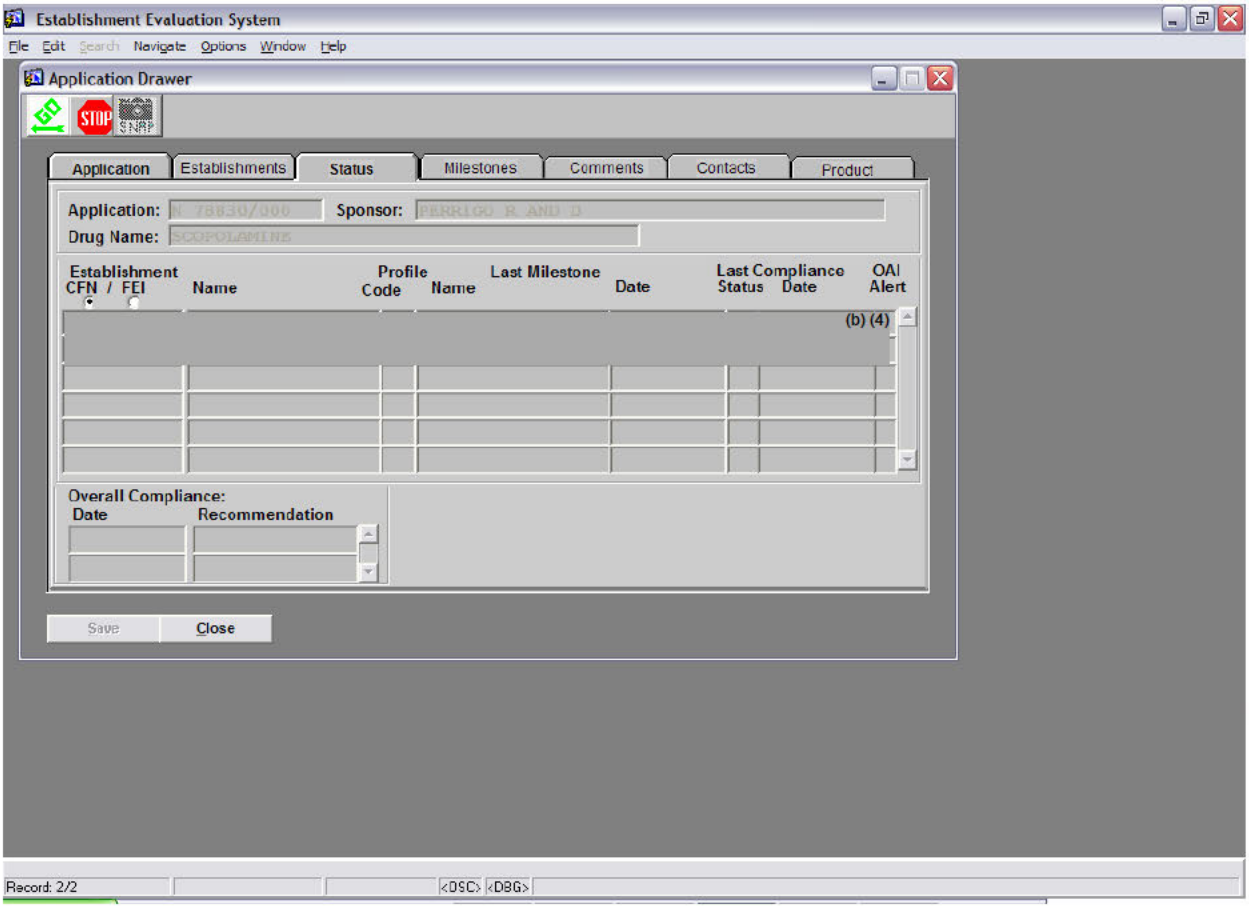
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CLINICAL REVIEW TEAM CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS

ANDA# _78-830_____ **FIRM NAME**_Perrigo R & D Companay_____

DRUG NAME ___Scopolamine T Therapeutic System, 1 mg/72 hr_____

DOSAGE FORM __Transdermal Patch_____

Requested by: __Washington, Edward_____ Date: _3/26/07_____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Clinical Review Team
X	**Study meets statutory requirements**
	Study does NOT meet statutory requirements
	Waiver meets statutory requirements
	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION: ___**COMPLETE** _**X**_ _**INCOMPLETE**

Reviewed by:

_____ Date: _____
Reviewer
Carol Y. Kim, Pharm.D.
Clinical Reviewer

_____ Date: _____
Dena R. Hixon, M.D.
Associate Director for Medical Affairs

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	X				Skin irritation, adhesion, and sensitization studies (#PRG-603) using test placebo patch
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				
PD Data Disk (or Elec Subm)	X				
Study Results	X				
Clinical Raw Data/ Medical Records	X				

Composition	X				Qualitatively and quantitatively not the same
BioStudy Lot Numbers	X				Test placebo patch lot number was provided.
Date of Manufacture	X				Manufacture date of the test placebo patch was provided.
Exp. Date of RLD		X			N/A
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			N/A

Additional Comments regarding the ANDA:

Comments to be conveyed to the sponsor:

You should provide literature references on scopolamine hypersensitivity or skin sensitization of the reference patch to document the degree of sensitization reported with use of the reference patch. Data presented in your skin sensitization study are not sufficient to compare the incidence of potential skin sensitization observed with the placebo patch to the incidence of sensitization known to occur with use of the reference patch.

Summary of the sponsor's skin irritation/sensitization/adhesion study

1. Data presented for skin irritation potential is acceptable for filing. The sponsor conducted a skin irritation study using the test placebo patch and mild irritant control (0.1% sodium lauryl sulfate solution applied to band-Aid). In this study, the test placebo patch was applied every 3 days to the same site behind the ear for 21 days. According to the sponsor's analysis, the cumulative mean skin irritation scores of the test placebo patch were no higher than those of the mild irritant control (upper 95% CI was less than zero).

2. Data presented for comparison of adhesion performance between the test and reference products are acceptable for filing.

   In the PK study (PRG-604), none of the test patches were detached (a score of 4). A score of 4 was observed in one reference patch approximately after 36 hours after dosing.

   Based on the sponsor's analysis, the test placebo patch detached 18 times over the first 72 hour application period (6.08% of the first patch applied). The study protocol states that no auxiliary tape or other substance should be applied to the patch to maintain adhesion.

3. Data presented for skin sensitization potential of the test placebo patch are not sufficient to compare the skin sensitization to that of the reference patch. Additional information will be requested and needs to be reviewed by the primary reviewer.

   Only the test placebo patch was tested in the skin sensitization analysis by the sponsor. According to the sponsor, if at any evaluation after application on Day 36 (challenge phase) scoring of irritation was greater than 4 (definite edema) on the dermal response scale or greater than 2 (marketed glazed appearance) on the "other effects scale", the subject was considered to have demonstrated a potential sensitization response. Based on the sponsor's analysis, no one demonstrated sensitization response. This definition of potential sensitization has not previously been accepted by the Clinical Review Team. The generally accepted definition of potential sensitization is an irritation score of 2 or higher or any "other effect" score above 0 at 24 hours or later following removal of the challenge patch. In the challenge phase, only one patient had a score of 2 at 48 and 72 hours after the challenge patch application. No one had a score greater than 2 in the challenge phase.

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 78-830 **FIRM NAME** **Perrigo R&D Company**

DRUG NAME Scopolamine Transdermal Therapeutic System

DOSAGE FORM **Transdermal Patch 1mg/72hr**
SUBJ: Request for examination of: Bioequivalence Study

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason: Not applicable no waiver requests included

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____ Date: _____
S. Christopher Jones
Reviewer

_____ Date: _____
Kuldeep Dhariwal
Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			Page 138 clinical study report
Assay Methodology	☒	☐			Pages 1-71 analytical study report
Procedure SOP	☒	☐			SOP included in submission
Methods Validation	☒	☐			Page 73 analytical study report
Study Results Ln/Lin	☒	☐			Throughout clinical study report
Adverse Events	☒	☐			Page 561 clinical study report
IRB Approval	☒	☐			Page 224 clinical study report
Dissolution Data	☒	☐			Section 3.2.P.2.2.1.3
Pre-screening of Patients	☒	☐			co-located with CRF's
Chromatograms	☒	☐			Page 191 analytical study report
Consent Forms	☒	☐			co-located with CRF's
Composition	☒	☐			Section 3.2.P.1.3
Summary of Study	☒	☐			Section 2.7.1
Individual Data & Graphs, Linear & Ln	☒	☐			Page 65 clinical summary report
PK/PD Data Disk Submitted)	☒	☐			SAS formatted located in EDR
Randomization Schedule	☒	☐			Page 298 clinical study report
Protocol Deviations	☒	☐			Page 407 clinical study report
Clinical Site	☒	☐			Section 2.7.1.1
Analytical Site	☒	☐			Section 2.7.1.1
Study Investigators	☒	☐			Page 253 clinical study report

Medical Records	☒	☐			Throughout clinical study report
Clinical Raw Data	☒	☐			Throughout clinical study report
Test Article Inventory	☒	☐			Found in "Patient-list-by-batch" section of the submission
BIO Batch Size	☒	☐			Section 3.2.R.1.P
Assay of Active Content Drug	☒	☐			Section 3.2.P.5.4
Content Uniformity	☒	☐			Section 3.2.P.5.4
Date of Manufacture	☒	☐			page 17 clinical study report
Exp. Date of RLD	☒	☐			page 17 clinical study report
BioStudy Lot Numbers	☒	☐			page 17 clinical study report
Statistics	☒	☐			page 303 clinical study report
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			page 26 clinical study report
Waiver requests for other strengths / supporting data	☐	☒			No waivers requested

Additional Comments regarding the ANDA:

The firm conducted a single dose bioequivalence study as well as an irritation, sensitization and adhesion study. This reviewer checked the BE study for completeness. OGD's clinical review division will review the irritation, sensitization and adhesion study. Confidence intervals in the BE study are close to lower limits for AUCt and AUCi AUCt 91.1 (81.2-102.2), AUCi 91.6 (82.2-102.0), Cmax 105.4 (92.0-120.7).

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/s/

Martin Shimer

5/24/2007 10:43:05 AM

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 78-830 **FIRM NAME** **Perrigo R&D Company**

DRUG NAME Scopolamine Transdermal Therapeutic System

DOSAGE FORM **Transdermal Patch 1mg/72hr**
SUBJ: Request for examination of: Bioequivalence Study

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☐	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason: Not applicable no waiver requests included

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____ Date: _____
S. Christopher Jones
Reviewer

_____ Date: _____
Kuldeep Dhariwal
Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐			Page 138 clinical study report
Assay Methodology	☒	☐			Pages 1-71 analytical study report
Procedure SOP	☒	☐			SOP included in submission
Methods Validation	☒	☐			Page 73 analytical study report
Study Results Ln/Lin	☒	☐			Throughout clinical study report
Adverse Events	☒	☐			Page 561 clinical study report
IRB Approval	☒	☐			Page 224 clinical study report
Dissolution Data	☒	☐			Section 3.2.P.2.2.1.3
Pre-screening of Patients	☒	☐			co-located with CRF's
Chromatograms	☒	☐			Page 191 analytical study report
Consent Forms	☒	☐			co-located with CRF's
Composition	☒	☐			Section 3.2.P.1.3
Summary of Study	☒	☐			Section 2.7.1
Individual Data & Graphs, Linear & Ln	☒	☐			Page 65 clinical summary report
PK/PD Data Disk Submitted)	☒	☐			SAS formatted located in EDR
Randomization Schedule	☒	☐			Page 298 clinical study report
Protocol Deviations	☒	☐			Page 407 clinical study report
Clinical Site	☒	☐			Section 2.7.1.1
Analytical Site	☒	☐			Section 2.7.1.1
Study Investigators	☒	☐			Page 253 clinical study report

Medical Records	☒	☐			Throughout clinical study report
Clinical Raw Data	☒	☐			Throughout clinical study report
Test Article Inventory	☒	☐			Found in "Patient-list-by-batch" section of the submission
BIO Batch Size	☒	☐			Section 3.2.R.1.P
Assay of Active Content Drug	☒	☐			Section 3.2.P.5.4
Content Uniformity	☒	☐			Section 3.2.P.5.4
Date of Manufacture	☒	☐			page 17 clinical study report
Exp. Date of RLD	☒	☐			page 17 clinical study report
BioStudy Lot Numbers	☒	☐			page 17 clinical study report
Statistics	☒	☐			page 303 clinical study report
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			page 26 clinical study report
Waiver requests for other strengths / supporting data	☐	☒			No waivers requested

Additional Comments regarding the ANDA:

The firm conducted a single dose bioequivalence study as well as an irritation, sensitization and adhesion study. This reviewer checked the BE study for completeness. OGD's clinical review division will review the irritation, sensitization and adhesion study. Confidence intervals in the BE study are close to lower limits for AUCt and AUCi AUCt 91.1 (81.2-102.2), AUCi 91.6 (82.2-102.0), Cmax 105.4 (92.0-120.7).

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/s/

Kuldeep R. Dhariwal

4/18/2007 03:14:18 PM

CLINICAL REVIEW TEAM CHECKLIST FOR GENERIC ANDA
FOR APPLICATION COMPLETENESS

ANDA# _78-830_____ **FIRM NAME**_Perrigo R & D Companay_____

DRUG NAME ___Scopolamine T Therapeutic System, 1 mg/72 hr_____

DOSAGE FORM __Transdermal Patch_____

Requested by: __Washington, Edward_____ Date: _3/26/07_____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Clinical Review Team
X	**Study meets statutory requirements**
	Study does NOT meet statutory requirements
	Waiver meets statutory requirements
	Waiver does NOT meet statutory requirements
	Reason:

RECOMMENDATION: **___COMPLETE** **_X_ _INCOMPLETE**

Reviewed by:

_____ Date: _____
Reviewer
Carol Y. Kim, Pharm.D.
Clinical Reviewer

_____ Date: _____
Dena R. Hixon, M.D.
Associate Director for Medical Affairs

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	X				Skin irritation, adhesion, and sensitization studies (#PRG-603) using test placebo patch
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				
PD Data Disk (or Elec Subm)	X				
Study Results	X				
Clinical Raw Data/ Medical Records	X				

Composition	X				Qualitatively and quantitatively not the same
BioStudy Lot Numbers	X				Test placebo patch lot number was provided.
Date of Manufacture	X				Manufacture date of the test placebo patch was provided.
Exp. Date of RLD		X			N/A
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			N/A

Additional Comments regarding the ANDA:

Comments to be conveyed to the sponsor:

You should provide literature references on scopolamine hypersensitivity or skin sensitization of the reference patch to document the degree of sensitization reported with use of the reference patch. Data presented in your skin sensitization study are not sufficient to compare the incidence of potential skin sensitization observed with the placebo patch to the incidence of sensitization known to occur with use of the reference patch.

Summary of the sponsor's skin irritation/sensitization/adhesion study

1. Data presented for skin irritation potential is acceptable for filing. The sponsor conducted a skin irritation study using the test placebo patch and mild irritant control (0.1% sodium lauryl sulfate solution applied to band-Aid). In this study, the test placebo patch was applied every 3 days to the same site behind the ear for 21 days. According to the sponsor's analysis, the cumulative mean skin irritation scores of the test placebo patch were no higher than those of the mild irritant control (upper 95% CI was less than zero).

2. Data presented for comparison of adhesion performance between the test and reference products are acceptable for filing.

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   Based on the sponsor's analysis, the test placebo patch detached 18 times over the first 72 hour application period (6.08% of the first patch applied). The study protocol states that no auxiliary tape or other substance should be applied to the patch to maintain adhesion.

3. Data presented for skin sensitization potential of the test placebo patch are not sufficient to compare the skin sensitization to that of the reference patch. Additional information will be requested and needs to be reviewed by the primary reviewer.

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/s/

Dena Hixon

4/18/2007 03:14:18 PM

M E M O R A N D U M

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

DATE : March 27, 2007

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 78-830 for Scopolamine Transdermal Extended Release Film, 1 mg/72 hr to determine if the application is substantially complete for filing.

Perrigo R&D Company has submitted ANDA 78-830 for Scopolamine Transdermal Extended Release Film, 1 mg/72 hr. It is a first generic. In order to accept an ANDA that contains a first generic, 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 Perrigo R&D Company on February 23, 2007 for its Scopolamine Transdermal Extended Release 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 Howard
3/27/2007 09:51:46 AM
APPLICATIONS EXA