CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21330/S-013

Trade name: Nicorette® Lozenge

Established name: nicotine polacrilex

Sponsor: GlaxoSmithKline Consumer Healthcare

Approval date: May 23, 2012

This supplemental NDA is submitted to:

- Fulfill the pediatric post-marketing commitment as required by the Pediatric Research and Equity Act (PREA).

- Add a bullet listing "if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you." in the Drug Facts section under the paragraph heading "Directions."

- Add a new 189-count Mint flavor "club pack" stock keeping unit to be marketed in 7 x 27-count "Poppac" immediate containers enclosed in a clear plastic blister attached to a backer card.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21330/S-013

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21330/S-013

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21330/S-013

SUPPLEMENT APPROVAL

GlaxoSmithKline Consumer Healthcare, L.P.
Attention: Iris H. Shelton
Associate Director, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Ms. Shelton:

Please refer to your Supplemental New Drug Application (sNDA) dated March 25, 2011, received July 29, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nicorette (nicotine polacrilex) lozenge, 2 mg and 4 mg.

We acknowledge receipt of your amendments dated April 14, April 21, August 9, September 7, September 8, 2011, January 31, February 10, March 26, and May 9, 2012.

This "Prior Approval" supplemental new drug application proposes the following:

- Addition of a bullet listing "if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you." in the Drug Facts section under the paragraph heading "Directions."
- A new 189 – count Mint flavor "club pack" stock keeping unit to be marketed in 7 x 27-count "Poppac" immediate containers enclosed in a clear plastic blister attached to a backer card.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

This "Prior Approval" supplemental new drug application also reports on the following postmarketing requirement listed in our October 31, 2002 approval letter.

0493-3 For the marketing of Commit™ (nicotine polacrilex lozenge), to reduce withdrawal symptoms, including nicotine craving, associated with quitting smoking, we are deferring submission of pediatric studies for patients 10-17 years until October 31, 2007. We are waiving the pediatric study requirement for this application for patients under age 10.

We have reviewed your submission and have determined that you are released from the above requirement. We are waiving the pediatric study requirement for this application because studies are impossible or highly impracticable.

This completes all of your postmarketing requirements and postmarketing commitments acknowledged in our October 31, 2002 letter.

LABELING

Submit final printed labeling as soon as they are available, but no more than 30 days after they are printed. The final printed labeling (FPL) must be identical to the enclosed labeling (27-count Mint flavor immediate container "Poppac" vial labels submitted on February 10, 2012, the 72-count Mint, Cherry and Cappuccino carton labels, the 108-count Original carton labels, and the 189-count Mint "club pack" backer cards (front and back panels) submitted on May 9, 2012), and must be in the "Drug Facts" format (21 CFR 201.66), where applicable.

Also include the consumer information leaflet (user guide), the 24-count vial immediate container labels, and 12-count blister card immediate container labels as part of the FPL for this supplement in order to maintain a record of the complete labeling for each stock keeping unit.

The final printed labeling should be submitted electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Labeling for approved NDA 21330/S-013**." Approval of this submission by FDA is not required before the labeling is used.

DRUG REGISTRATION AND LISTING

All drug establishment registration and drug listing information is to be submitted to FDA electronically, via the FDA automated system for processing structured product labeling (SPL) files (eLIST). At the time that you submit your final printed labeling (FPL), the content of labeling (Drug Facts) should be submitted in SPL format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. In addition, representative container or carton labeling, whichever includes Drug Facts, (where differences exist only in the quantity of contents statement) should be submitted as a JPG file.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Phong Do, Regulatory Project Manager, at (301) 796-4795.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURES:
Carton and Container Labeling

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

/s/

JOEL SCHIFFENBAUER
05/23/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21330/S-013

LABELING

In case of overdose, get medical help or contact a Poison Control Center right away.

Retain outer carton for full product uses, directions and warnings. Discard POPPAC after use.

Tamper Evident Feature: Do not use if clear neckband printed "SEALED FOR SAFETY" is missing or broken.

Distributed By:
GlaxoSmithKline Consumer Healthcare, L.P.
Moon Township, PA 15108
Made in Switzerland.

101449XA

27 LOZENGES

To open vial, push in child resistant band on the POPPAC® with thumb.

Flip up the top of the POPPAC® and remove lozenge.

A small amount of powder on opening of the POPPAC® is normal.

Nicorette®

nicotine polacrilex lozenge, 2mg · stop smoking aid

Lozenge

Mint

Directions:

Not for Individual Sale

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

Place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. Do not chew or swallow lozenge. Occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20 - 30 minutes). Do not eat or drink 15 minutes before using or while the lozenge is in your mouth.

Do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.

Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash.

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In case of overdose, get medical help or contact a Poison Control Center right away.

Retain outer carton for full product uses, directions and warnings. Discard POPPAC after use.

Tamper Evident Feature: Do not use if clear neckband printed "SEALED FOR SAFETY" is missing or broken.

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GlaxoSmithKline Consumer Healthcare, L.P.
Moon Township, PA 15108
Made in Switzerland.

101447XA

27 LOZENGES

To open vial, push in child resistant band on the POPPAC® with thumb.

Flip up the top of the POPPAC® and remove lozenge.

A small amount of powder on opening of the POPPAC® is normal.

Nicorette®

nicotine polacrilex lozenge, 4mg · stop smoking aid

Lozenge

Mint

Directions:

Not for Individual Sale

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

Place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. Do not chew or swallow lozenge. Occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20 - 30 minutes). Do not eat or drink 15 minutes before using or while the lozenge is in your mouth.

Do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.

Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash.

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Lot
Exp

Drug Facts (continued)

- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

- **nicotine lozenge is a medicine and must be used a certain way to get the best results**
- place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20 - 30 minutes). Minimize swallowing. **Do not chew or swallow lozenge.**
- you may feel a warm or tingling sensation
- occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20 - 30 minutes)
- do not eat or drink 15 minutes before using or while the lozenge is in your mouth
- to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
- do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
- **do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.**
- stop using the nicotine lozenge at the end of 12 weeks. If you still feel the need to use nicotine lozenges, talk to your doctor.

Other information

- **each lozenge contains:** sodium, 18mg
- Phenylketonurics: Contains Phenylalanine 3.4 mg per lozenge
- store at 20 - 25°C (68 - 77°F)
- keep POPPAC tightly closed and protect from light

Inactive ingredients

acacia, aspartame, calcium polycarbophil, corn syrup solids, flavors, lactose, magnesium stearate, maltodextrin, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, soy protein, triethyl citrate, xanthan gum

Questions or comments?

call toll-free **1-888-569-1743** (English/Spanish) weekdays (9:00 am - 4:30 pm ET)

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GlaxoSmithKline Consumer Healthcare, L.P.
Moon Township, PA 15108, Made in Switzerland.

NDC 0135-0510-01

Nicorette®

nicotine polacrilex lozenge, 2mg • stop smoking aid

Lozenge

Includes User's Guide

2 mg

FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE MORE THAN 30 MINUTES AFTER WAKING UP.
If you smoke your first cigarette **WITHIN 30 MINUTES** of waking up, use Nicorette 4mg Lozenge

Mint

72 LOZENGES, 2mg Each
(3 Poppac™ Containers of 24)

- **not for sale to those under 18 years of age**
- **proof of age required**
- **not for sale in vending machines or from any source where proof of age cannot be verified**

TAMPER EVIDENT FEATURE: Do not use if clear neckband printed "SEALED FOR SAFETY" is missing or broken.
Retain outer carton for full product uses, directions and warnings.

TO INCREASE YOUR SUCCESS IN QUITTING:

1. You must be motivated to quit.
2. **Use Enough** - Use **at least 9 lozenges** of Nicorette per day during the first six weeks.
3. **Use Long Enough** - Use Nicorette for the full 12 weeks.
4. **Use With a Support Program** as directed in the enclosed User's Guide.

Nicorette® POPPAC™

To open vial, push in child resistant band on the POPPAC with thumb.

Flip up the top of the POPPAC and remove lozenge. A small amount of powder on opening of the POPPAC is normal.

For more information and for a FREE individualized stop smoking program, please visit www.Nicorette.com or see inside for more details.

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EAS TAGGED

Drug Facts

Active ingredient (in each lozenge) — *Purpose*

Nicotine polacrilex, 2mg ..... Stop smoking aid

Use • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Do not use
- if you continue to smoke, chew tobacco, use snuff, or use a nicotine patch or other nicotine containing products

Ask a doctor before use if you have
- a sodium-restricted diet
- heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcer or diabetes

Ask a doctor or pharmacist before use if you are
- using a non-nicotine stop smoking drug
- taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

Stop use and ask a doctor if
- mouth problems occur
- persistent indigestion or severe sore throat occurs
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat

Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.**
- before using this product, read the enclosed User's Guide for complete directions and other important information
- stop smoking completely when you begin using the lozenge
- **if you smoke your first cigarette within 30 minutes of waking up,** use 4mg nicotine lozenge

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Varnish K.O.

PS

PLACE ANTI-THEFT STICKER HERE

THEFT SURVEILLANCE TAG AREA

Glue area - No Varnish

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Drug Facts (continued)

- **if you smoke your first cigarette within 30 minutes of waking up,** use 4mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

- **nicotine lozenge is a medicine and must be used a certain way to get the best results**
- place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20 - 30 minutes). Minimize swallowing. **Do not chew or swallow lozenge.**
- you may feel a warm or tingling sensation
- occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20 - 30 minutes)
- do not eat or drink 15 minutes before using or while the lozenge is in your mouth
- to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
- do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
- **do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.**
- stop using the nicotine lozenge at the end of 12 weeks. If you still feel the need to use nicotine lozenges, talk to your doctor.

Other information

- **each lozenge contains:** sodium, 18mg
- Phenylketonurics: Contains Phenylalanine 3.4 mg per lozenge
- store at 20 - 25°C (68 - 77°F)
- keep POPPAC tightly closed and protect from light

Inactive ingredients

acacia, aspartame, calcium polycarbophil, corn syrup solids, flavors, lactose, magnesium stearate, maltodextrin, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, soy protein, triethyl citrate, xanthan gum

Questions or comments?

call toll-free **1-888-569-1743**
(English/Spanish) weekdays (9:00 am - 4:30 pm ET)

Distributed By:
GlaxoSmithKline Consumer Healthcare, L.P.
Moon Township, PA 15108, Made in Switzerland.

PS

NDC 0135-0511-01

Nicorette®

nicotine polacrilex lozenge, 4mg • stop smoking aid

Lozenge

Includes User's Guide

4 mg

FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE WITHIN 30 MINUTES OF WAKING UP.

If you smoke your first cigarette **MORE THAN 30 MINUTES** after waking up, use Nicorette 2mg Lozenge

Mint

72 LOZENGES, 4mg Each
(3 Poppac™ Containers of 24)

PLACE ANTI-THEFT STICKER HERE

THEFT SURVEILLANCE TAG AREA

- **not for sale to those under 18 years of age**
- **proof of age required**
- **not for sale in vending machines or from any source where proof of age cannot be verified**

TAMPER EVIDENT FEATURE: Do not use if clear neckband printed "SEALED FOR SAFETY" is missing or broken.
Retain outer carton for full product uses, directions and warnings.

TO INCREASE YOUR SUCCESS IN QUITTING:

1. You must be motivated to quit.
2. **Use Enough** - Use **at least 9 lozenges** of Nicorette per day during the first six weeks.
3. **Use Long Enough** - Use Nicorette for the full 12 weeks.
4. **Use With a Support Program** as directed in the enclosed User's Guide.

Nicorette® POPPAC™

To open vial, push in child resistant band on the POPPAC with thumb.

Flip up the top of the POPPAC and remove lozenge. A small amount of powder on opening of the POPPAC is normal.

For more information and for a FREE individualized stop smoking program, please visit www.Nicorette.com or see inside for more details.

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EAS TAGGED

Drug Facts

Active ingredient (in each lozenge) — **Purpose**
Nicotine polacrilex, 4mg ..... Stop smoking aid

Use • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Do not use
- if you continue to smoke, chew tobacco, use snuff, or use a nicotine patch or other nicotine containing products

Ask a doctor before use if you have
- a sodium-restricted diet
- heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcer or diabetes

Ask a doctor or pharmacist before use if you are
- using a non-nicotine stop smoking drug
- taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

Stop use and ask a doctor if
- mouth problems occur
- persistent indigestion or severe sore throat occurs
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat

Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.**
- before using this product, read the enclosed User's Guide for complete directions and other important information
- stop smoking completely when you begin using the lozenge
- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2mg nicotine lozenge ▶

Varnish K.O.

Glue area - No Varnish

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Reference ID: 3135194

Drug Facts (continued)

- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

- **nicotine lozenge is a medicine and must be used a certain way to get the best results**
- place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20 - 30 minutes). Minimize swallowing. **Do not chew or swallow lozenge.**
- you may feel a warm or tingling sensation
- occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20 - 30 minutes)
- do not eat or drink 15 minutes before using or while the lozenge is in your mouth
- to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
- do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
- **do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenge per day.**
- stop using the nicotine lozenge at the end of 12 weeks. If you still feel the need to use nicotine lozenges, talk to your doctor.

Other information

- **each lozenge contains:** sodium, 18mg
- store at 20 - 25°C (68 - 77°F)
- keep POPPAC tightly closed and protect from light

Inactive ingredients

acesulfame potassium, benzyl alcohol, butylhydroxy toluene, calcium polycarbophil, coconut and/or palm kernel oil, eugenol, flavors, magnesium stearate, maltodextrin, mannitol, modified corn starch, potassium bicarbonate, sodium alginate, sodium carbonate, xanthan gum

Questions or comments?

call toll-free **1-888-569-1743**
(English/Spanish) weekdays (9:00 am - 4:30 pm ET)

Distributed By:
GlaxoSmithKline Consumer Healthcare, L.P.
Moon Township, PA 15108, Made in Switzerland.

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NDC 0135-0512-01

Nicorette®

nicotine polacrilex lozenge, 2mg • stop smoking aid

Lozenge

Includes User's Guide

2 mg

FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE MORE THAN 30 MINUTES AFTER WAKING UP.
If you smoke your first cigarette WITHIN 30 MINUTES of waking up, use Nicorette 4mg Lozenge

Cherry

72 LOZENGES, 2mg Each
(3 Poppac™ Containers of 24)

PLACE ANTI-THEFT STICKER HERE

THEFT SURVEILLANCE TAG AREA

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Nicorette® POPPAC™

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For more information and for a FREE individualized stop smoking program, please visit www.Nicorette.com or see inside for more details.

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EAS TAGGED

Drug Facts

Active ingredient (in each lozenge) — **Purpose**
Nicotine polacrilex, 2mg ..... Stop smoking aid

Use • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Do not use
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Directions

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- stop smoking completely when you begin using the lozenge
- **if you smoke your first cigarette within 30 minutes of waking up,** use 4mg nicotine lozenge ▶

Varnish K.O.

Glue area - No Varnish

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Reference ID: 3135194

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Drug Facts (continued)

- **if you smoke your first cigarette within 30 minutes of waking up,** use 4mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
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Other information

- **each lozenge contains:** sodium, 18mg
- store at 20 - 25°C (68 - 77°F)
- keep POPPAC tightly closed and protect from light

Inactive ingredients

acesulfame potassium, benzyl alcohol, butylhydroxy toluene, calcium polycarbophil, coconut and/or palm kernel oil, eugenol, flavors, magnesium stearate, maltodextrin, mannitol, modified corn starch, potassium bicarbonate, sodium alginate, sodium carbonate, xanthan gum

Questions or comments?

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(English/Spanish) weekdays (9:00 am - 4:30 pm ET)

Distributed By:
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Moon Township, PA 15108, Made in Switzerland.

PS

NDC 0135-0513-01

Nicorette®

nicotine polacrilex lozenge, 4mg • stop smoking aid

Lozenge

Includes User's Guide

4 mg

FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE WITHIN 30 MINUTES OF WAKING UP.

If you smoke your first cigarette **MORE THAN 30 MINUTES** after waking up, use Nicorette 2mg Lozenge

Cherry

72 LOZENGES, 4mg Each
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- **proof of age required**
- **not for sale in vending machines or from any source where proof of age cannot be verified**

TAMPER EVIDENT FEATURE: Do not use if clear neckband printed "SEALED FOR SAFETY" is missing or broken.
Retain outer carton for full product uses, directions and warnings.

TO INCREASE YOUR SUCCESS IN QUITTING:

1. You must be motivated to quit.
2. **Use Enough** - Use **at least 9 lozenges** of Nicorette per day during the first six weeks.
3. **Use Long Enough** - Use Nicorette for the full 12 weeks.
4. **Use With a Support Program** as directed in the enclosed User's Guide.

Nicorette® POPPAC™

To open vial, push in child resistant band on the POPPAC with thumb.

Flip up the top of the POPPAC and remove lozenge. A small amount of powder on opening of the POPPAC is normal.

For more information and for a FREE individualized stop smoking program, please visit www.Nicorette.com or see inside for more details.

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EAS TAGGED

Drug Facts

Active ingredient (in each lozenge) — **Purpose**
Nicotine polacrilex, 4mg ..... Stop smoking aid

Use • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Do not use
- if you continue to smoke, chew tobacco, use snuff, or use a nicotine patch or other nicotine containing products

Ask a doctor before use if you have
- a sodium-restricted diet
- heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcer or diabetes

Ask a doctor or pharmacist before use if you are
- using a non-nicotine stop smoking drug
- taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

Stop use and ask a doctor if
- mouth problems occur
- persistent indigestion or severe sore throat occurs
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat

Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.**
- before using this product, read the enclosed User's Guide for complete directions and other important information
- stop smoking completely when you begin using the lozenge
- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2mg nicotine lozenge

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Reference ID: 3135194

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Drug Facts (continued)

- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

- **nicotine lozenge is a medicine and must be used a certain way to get the best results**
- place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20 - 30 minutes). Minimize swallowing. **Do not chew or swallow lozenge.**
- you may feel a warm or tingling sensation
- occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20 - 30 minutes)
- do not eat or drink 15 minutes before using or while the lozenge is in your mouth
- to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
- do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
- **do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.**
- stop using the nicotine lozenge at the end of 12 weeks. If you still feel the need to use nicotine lozenges, talk to your doctor.

Other information

- **each lozenge contains:** sodium, 18mg
- store at 20 - 25°C (68 - 77°F)
- keep POPPAC tightly closed and protect from light

Inactive ingredients

acesulfame potassium, butylhydroxy toluene, calcium polycarbophil, flavor, magnesium stearate, maltodextrin, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, xanthan gum

Questions or comments?

call toll-free **1-888-569-1743** (English/Spanish) weekdays (9:00 am - 4:30 pm ET)

Distributed By:
GlaxoSmithKline Consumer Healthcare, L.P.
Moon Township, PA 15108, Made in Switzerland.

Nicorette®

nicotine polacrilex lozenge, 2mg • stop smoking aid

Lozenge

Includes User's Guide

2 mg

FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE MORE THAN 30 MINUTES AFTER WAKING UP.
If you smoke your first cigarette **WITHIN 30 MINUTES** of waking up, use Nicorette 4mg Lozenge

Cappuccino

72 LOZENGES, 2mg Each
(3 Poppac™ Containers of 24)

- **not for sale to those under 18 years of age**
- **proof of age required**
- **not for sale in vending machines or from any source where proof of age cannot be verified**

TAMPER EVIDENT FEATURE: Do not use if clear neckband printed "SEALED FOR SAFETY" is missing or broken.
Retain outer carton for full product uses, directions and warnings.

TO INCREASE YOUR SUCCESS IN QUITTING:

1. You must be motivated to quit.
2. **Use Enough** - Use **at least 9 lozenges** of Nicorette per day during the first six weeks.
3. **Use Long Enough -** Use Nicorette for the full 12 weeks.
4. **Use With a Support Program** as directed in the enclosed User's Guide.

Nicorette® POPPAC™

To open vial, push in child resistant band on the POPPAC with thumb.

Flip up the top of the POPPAC and remove lozenge. A small amount of powder on opening of the POPPAC is normal.

For more information and for a FREE individualized stop smoking program, please visit www.Nicorette.com or see inside for more details.

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Drug Facts

Active ingredient (in each lozenge) — Purpose

Nicotine polacrilex, 2mg ..... Stop smoking aid

Use • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Do not use
- if you continue to smoke, chew tobacco, use snuff, or use a nicotine patch or other nicotine containing products

Ask a doctor before use if you have
- a sodium-restricted diet
- heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcer or diabetes

Ask a doctor or pharmacist before use if you are
- using a non-nicotine stop smoking drug
- taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

Stop use and ask a doctor if
- mouth problems occur
- persistent indigestion or severe sore throat occurs
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat

Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.**
- before using this product, read the enclosed User's Guide for complete directions and other important information
- stop smoking completely when you begin using the lozenge
- **if you smoke your first cigarette within 30 minutes of waking up,** use 4mg nicotine lozenge

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Varnish K.O.

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PLACE ANTI-THEFT STICKER HERE

THEFT SURVEILLANCE TAG AREA

Glue area - No Varnish

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Drug Facts (continued)

- **if you smoke your first cigarette within 30 minutes of waking up,** use 4mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

- **nicotine lozenge is a medicine and must be used a certain way to get the best results**
- place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20 - 30 minutes). Minimize swallowing. **Do not chew or swallow lozenge.**
- you may feel a warm or tingling sensation
- occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20 - 30 minutes)
- do not eat or drink 15 minutes before using or while the lozenge is in your mouth
- to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
- do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
- **do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.**
- stop using the nicotine lozenge at the end of 12 weeks. If you still feel the need to use nicotine lozenges, talk to your doctor.

Other information

- **each lozenge contains:** sodium, 18mg
- store at 20 - 25°C (68 - 77°F)
- keep POPPAC tightly closed and protect from light

Inactive ingredients acesulfame potassium, butylhydroxy toluene, calcium polycarbophil, flavor, magnesium stearate, maltodextrin, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, xanthan gum

Questions or comments? call toll-free **1-888-569-1743** (English/Spanish) weekdays (9:00 am - 4:30 pm ET)

Distributed By:
GlaxoSmithKline Consumer Healthcare, L.P.
Moon Township, PA 15108, Made in Switzerland.

PS

Nicorette®

nicotine polacrilex lozenge, 4mg • stop smoking aid

Lozenge

Includes User's Guide

4 mg

FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE WITHIN 30 MINUTES OF WAKING UP.

If you smoke your first cigarette **MORE THAN 30 MINUTES** after waking up, use Nicorette 2mg Lozenge

Cappuccino

72 LOZENGES, 4mg Each

(3 Poppac™ Containers of 24)

PLACE ANTI-THEFT STICKER HERE

THEFT SURVEILLANCE TAG AREA

- **not for sale to those under 18 years of age**
- **proof of age required**
- **not for sale in vending machines or from any source where proof of age cannot be verified**

TAMPER EVIDENT FEATURE: Do not use if clear neckband printed "SEALED FOR SAFETY" is missing or broken.
Retain outer carton for full product uses, directions and warnings.

TO INCREASE YOUR SUCCESS IN QUITTING:

1. You must be motivated to quit.
2. **Use Enough** - Use **at least 9 lozenges** of Nicorette per day during the first six weeks.
3. **Use Long Enough -** Use Nicorette for the full 12 weeks.
4. **Use With a Support Program** as directed in the enclosed User's Guide.

Nicorette® POPPAC™

To open vial, push in child resistant band on the POPPAC with thumb.

Flip up the top of the POPPAC and remove lozenge. A small amount of powder on opening of the POPPAC is normal.

For more information and for a FREE individualized stop smoking program, please visit www.Nicorette.com or see inside for more details.

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Drug Facts

Active ingredient (in each lozenge) — **Purpose**

Nicotine polacrilex, 4mg ..... Stop smoking aid

Use • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Do not use
- if you continue to smoke, chew tobacco, use snuff, or use a nicotine patch or other nicotine containing products

Ask a doctor before use if you have
- a sodium-restricted diet
- heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcer or diabetes

Ask a doctor or pharmacist before use if you are
- using a non-nicotine stop smoking drug
- taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

Stop use and ask a doctor if
- mouth problems occur
- persistent indigestion or severe sore throat occurs
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat

Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.**
- before using this product, read the enclosed User's Guide for complete directions and other important information
- stop smoking completely when you begin using the lozenge
- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2mg nicotine lozenge

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Varnish K.O.

Glue area - No Varnish

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Reference ID: 3135194

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To remove the lozenge, tear off single unit.

Peel off backing starting at corner with loose edge.

Push lozenge through foil.

Drug Facts (continued)

- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

- **nicotine lozenge is a medicine and must be used a certain way to get the best results**
- place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20 - 30 minutes). Minimize swallowing. **Do not chew or swallow lozenge.**
- you may feel a warm or tingling sensation
- occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20 - 30 minutes)
- do not eat or drink 15 minutes before using or while the lozenge is in your mouth
- to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
- do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
- **do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.**
- stop using the nicotine lozenge at the end of 12 weeks. If you still feel the need to use nicotine lozenges, talk to your doctor.

Other information

- **each lozenge contains:** sodium, 18mg
- Phenylketonurics: Contains Phenylalanine 3.4 mg per lozenge
- store at 20 - 25°C (68 - 77°F)
- protect from light

Inactive ingredients

aspartame, calcium polycarbophil, flavor, magnesium stearate, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, xanthan gum

Questions or comments?

call toll-free **1-888-569-1743** (English/Spanish) weekdays (9:00 am - 4:30 pm ET)

Distributed By:
GlaxoSmithKline Consumer Healthcare, L.P.
Moon Township, PA 15108, Made in Switzerland.

NDC 0135-0514-03

Nicorette®

nicotine polacrilex lozenge, 2mg • stop smoking aid

Lozenge

Includes User's Guide

2 mg

FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE MORE THAN 30 MINUTES AFTER WAKING UP.
If you smoke your first cigarette **WITHIN 30 MINUTES** of waking up, use Nicorette 4mg Lozenge

Original

108 LOZENGES, 2mg Each

PLACE ANTI-THEFT STICKER HERE

THEFT SURVEILLANCE TAG AREA

- **not for sale to those under 18 years of age**
- **proof of age required**
- **not for sale in vending machines or from any source where proof of age cannot be verified**

This product is protected in sealed blisters.
Do not use if individual blisters or printed backings are broken, open, or torn.

TO INCREASE YOUR SUCCESS IN QUITTING:

1. You must be motivated to quit.
2. **Use Enough** - Use **at least 9 lozenges** of Nicorette per day during the first six weeks.
3. **Use Long Enough** - Use Nicorette for the full 12 weeks.
4. **Use With a Support Program** as directed in the enclosed User's Guide.

For more information and for a FREE individualized stop smoking program, please visit www.Nicorette.com or see inside for more details.

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Internal theft surveillance system
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PS

Drug Facts

Active ingredient (in each lozenge) — **Purpose**
Nicotine polacrilex, 2mg ..... Stop smoking aid

Use • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Do not use
- if you continue to smoke, chew tobacco, use snuff, or use a nicotine patch or other nicotine containing products

Ask a doctor before use if you have
- a sodium-restricted diet
- heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcer or diabetes

Ask a doctor or pharmacist before use if you are
- using a non-nicotine stop smoking drug
- taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

Stop use and ask a doctor if
- mouth problems occur
- persistent indigestion or severe sore throat occurs
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat

Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.**
- before using this product, read the enclosed User's Guide for complete directions and other important information
- stop smoking completely when you begin using the lozenge
- **if you smoke your first cigarette within 30 minutes of waking up,** use 4mg nicotine lozenge

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Reference ID: 3135194

To remove the lozenge, tear off single unit.

Peel off backing starting at corner with loose edge.

Push lozenge through foil.

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VARNISH KNOCK OUT AREA. NO COPY AREA.

Drug Facts (continued)

- **if you smoke your first cigarette within 30 minutes of waking up,** use 4mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

- **nicotine lozenge is a medicine and must be used a certain way to get the best results**
- place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20 - 30 minutes). Minimize swallowing. **Do not chew or swallow lozenge.**
- you may feel a warm or tingling sensation
- occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20 - 30 minutes)
- do not eat or drink 15 minutes before using or while the lozenge is in your mouth
- to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
- do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
- **do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.**
- stop using the nicotine lozenge at the end of 12 weeks. If you still feel the need to use nicotine lozenges, talk to your doctor.

Other information

- **each lozenge contains:** sodium, 18mg
- Phenylketonurics: Contains Phenylalanine 3.4 mg per lozenge
- store at 20 - 25°C (68 - 77°F)
- protect from light

Inactive ingredients

aspartame, calcium polycarbophil, flavor, magnesium stearate, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, xanthan gum

Questions or comments?

call toll-free **1-888-569-1743** (English/Spanish) weekdays (9:00 am - 4:30 pm ET)

Distributed By:
GlaxoSmithKline Consumer Healthcare, L.P.
Moon Township, PA 15108, Made in Switzerland.

NDC 0135-0515-03

Nicorette®

nicotine polacrilex lozenge, 4mg • stop smoking aid

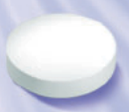
Lozenge

Includes User's Guide

4 mg

FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE WITHIN 30 MINUTES OF WAKING UP.

If you smoke your first cigarette **MORE THAN 30 MINUTES** after waking up, use Nicorette 2mg Lozenge



Original

108 LOZENGES, 4mg Each

- **not for sale to those under 18 years of age**
- **proof of age required**
- **not for sale in vending machines or from any source where proof of age cannot be verified**

This product is protected in sealed blisters.
Do not use if individual blisters or printed backings are broken, open, or torn.

TO INCREASE YOUR SUCCESS IN QUITTING:

1. You must be motivated to quit.
2. **Use Enough** - Use **at least 9 lozenges** of Nicorette per day during the first six weeks.
3. **Use Long Enough** - Use Nicorette for the full 12 weeks.
4. **Use With a Support Program** as directed in the enclosed User's Guide.

For more information and for a FREE individualized stop smoking program, please visit www.Nicorette.com or see inside for more details.

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Internal theft surveillance system
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PLACE ANTI-THEFT STICKER HERE

THEFT SURVEILLANCE TAG AREA

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Drug Facts

Active ingredient (in each lozenge) — **Purpose**
Nicotine polacrilex, 4mg ..... Stop smoking aid

Use • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Do not use
- if you continue to smoke, chew tobacco, use snuff, or use a nicotine patch or other nicotine containing products

Ask a doctor before use if you have
- a sodium-restricted diet
- heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcer or diabetes

Ask a doctor or pharmacist before use if you are
- using a non-nicotine stop smoking drug
- taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

Stop use and ask a doctor if
- mouth problems occur
- persistent indigestion or severe sore throat occurs
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat

Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.**
- before using this product, read the enclosed User's Guide for complete directions and other important information
- stop smoking completely when you begin using the lozenge
- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2mg nicotine lozenge

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LEAVE AREA WHITE

VARNISH KNOCK OUT AREA. NO COPY AREA.

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Reference ID: 3135194

NDC 0135-0510-03

Nicorette®

nicotine polacrilex lozenge, 2mg · stop smoking aid

Lozenge

Includes User's Guide

2 mg

FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE MORE THAN 30 MINUTES AFTER WAKING UP.

If you smoke your first cigarette **WITHIN 30 MINUTES** of waking up, use Nicorette 4mg Lozenge

Mint

189 LOZENGES
2mg EACH
(7 Poppac® Containers of 27)

NOTE: THIS AREA TO BE DIECUT AFTER PRINTING PROCESS.
GRAPHICS SHOULD BE EXTENDED INTO THIS AREA PER REQUEST OF PRINT, BUT NO COPY.

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189 LOZENGES
2mg EACH
(7 Poppac® Containers of 27)

Reference ID: 3135194

Nicorette®

nicotine polacrilex lozenge, 2mg • stop smoking aid

Lozenge

Nicorette® POPPAC®

To open vial, push in child resistant band on the POPPAC with thumb.

Flip up the top of the POPPAC and remove lozenge. A small amount of powder on opening of the POPPAC is normal.

Personalized Quit Plan

Visit **www.Nicorette.com** to enroll in a free, personalized quit plan. **Nicorette Committed Quitters** is a personalized stop smoking program that will help you understand your smoking habits and determine how to best overcome your cravings. Track, target, and tame your temptations with **Nicorette Committed Quitters.** Only available at **www.Nicorette.com**

Drug Facts

Active ingredient (in each lozenge) — **Purpose**

Nicotine polacrilex, 2mg ..... Stop smoking aid

Use • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Do not use

- if you continue to smoke, chew tobacco, use snuff, or use a nicotine patch or other nicotine containing products

Ask a doctor before use if you have

- a sodium-restricted diet
- heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcer or diabetes

Ask a doctor or pharmacist before use if you are

- using a non-nicotine stop smoking drug
- taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

Stop use and ask a doctor if

- mouth problems occur
- persistent indigestion or severe sore throat occurs
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat

Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.** ▶

Drug Facts (continued)

- before using this product, read the enclosed User's Guide for complete directions and other important information
- stop smoking completely when you begin using the lozenge
- **if you smoke your first cigarette within 30 minutes of waking up,** use 4mg nicotine lozenge
- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

- **nicotine lozenge is a medicine and must be used a certain way to get the best results**
- place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20 - 30 minutes). Minimize swallowing. **Do not chew or swallow lozenge.**
- you may feel a warm or tingling sensation
- occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20 - 30 minutes)
- do not eat or drink 15 minutes before using or while the lozenge is in your mouth
- to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
- do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
- **do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.**
- stop using the nicotine lozenge at the end of 12 weeks. If you still feel the need to use nicotine lozenges, talk to your doctor.

Other information

- **each lozenge contains:** sodium, 18mg
- Phenylketonurics: Contains Phenylalanine 3.4mg per lozenge
- store at 20 - 25°C (68 - 77°F)
- keep POPPAC tightly closed and protect from light

Inactive ingredients acacia, aspartame, calcium polycarbophil, corn syrup solids, flavors, lactose, magnesium stearate, maltodextrin, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, soy protein, triethyl citrate, xanthan gum

Questions or comments? call toll-free **1-888-569-1743** (English/Spanish) weekdays (9:00 am - 4:30 pm ET)

TO INCREASE YOUR SUCCESS IN QUITTING:

1. You must be motivated to quit.
2. **Use Enough** - Use **at least 9** lozenges of Nicorette per day during the first six weeks.
3. **Use Long Enough** - Use Nicorette for the full 12 weeks.
4. **Use With a Support Program** as directed in the enclosed User's Guide.

- **not for sale to those under 18 years of age**
- **proof of age required**
- **not for sale in vending machines or from any source where proof of age cannot be verified**

TAMPER EVIDENT FEATURE: Do not use if clear neckband printed "SEALED FOR SAFETY" is missing or broken. Retain outer back panel for full product uses, directions and warnings.

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Distributed By:
GlaxoSmithKline Consumer Healthcare, L.P.
Moon Township, PA 15108, Made in Switzerland

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Lot:
Exp:

NDC 0135-0511-03

Nicorette®

nicotine polacrilex lozenge, 4mg · stop smoking aid

Lozenge

Includes User's Guide

4 mg

FOR THOSE WHO SMOKE THEIR FIRST CIGARETTE WITHIN 30 MINUTES OF WAKING UP.

If you smoke your first cigarette **MORE THAN 30 MINUTES** after waking up, use Nicorette 2mg Lozenge

Mint

189 LOZENGES
4mg EACH
(7 Poppac® Containers of 27)

NOTE: THIS AREA TO BE DIECUT AFTER PRINTING PROCESS.
GRAPHICS SHOULD BE EXTENDED INTO THIS AREA PER REQUEST OF PRINT, BUT NO COPY.

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189 LOZENGES
4mg EACH
(7 Poppac® Containers of 27)

Reference ID: 3135194

Nicorette®

nicotine polacrilex lozenge, 4mg • stop smoking aid

Lozenge

Nicorette® POPPAC®

To open vial, push in child resistant band on the POPPAC with thumb.

Flip up the top of the POPPAC and remove lozenge. A small amount of powder on opening of the POPPAC is normal.

Personalized Quit Plan

Visit **www.Nicorette.com** to enroll in a free, personalized quit plan. **Nicorette Committed Quitters** is a personalized stop smoking program that will help you understand your smoking habits and determine how to best overcome your cravings. Track, target, and tame your temptations with **Nicorette Committed Quitters.** Only available at **www.Nicorette.com**

Drug Facts

Active ingredient (in each lozenge) ***Purpose***

Nicotine polacrilex, 4mg ..... Stop smoking aid

Use • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Do not use

- if you continue to smoke, chew tobacco, use snuff, or use a nicotine patch or other nicotine containing products

Ask a doctor before use if you have

- a sodium-restricted diet
- heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcer or diabetes

Ask a doctor or pharmacist before use if you are

- using a non-nicotine stop smoking drug
- taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

Stop use and ask a doctor if

- mouth problems occur
- persistent indigestion or severe sore throat occurs
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat

Keep out of reach of children and pets. Nicotine lozenges may have enough nicotine to make children and pets sick. If you need to remove the lozenge, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.** ▶

Drug Facts (continued)

- before using this product, read the enclosed User's Guide for complete directions and other important information
- stop smoking completely when you begin using the lozenge
- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2mg nicotine lozenge
- **if you smoke your first cigarette within 30 minutes of waking up,** use 4mg nicotine lozenge according to the following 12 week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

- **nicotine lozenge is a medicine and must be used a certain way to get the best results**
- place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20 - 30 minutes). Minimize swallowing. **Do not chew or swallow lozenge.**
- you may feel a warm or tingling sensation
- occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20 - 30 minutes)
- do not eat or drink 15 minutes before using or while the lozenge is in your mouth
- to improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks
- do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, nausea or other side effects
- **do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.**
- stop using the nicotine lozenge at the end of 12 weeks. If you still feel the need to use nicotine lozenges, talk to your doctor.

Other information

- **each lozenge contains:** sodium, 18mg
- Phenylketonurics: Contains Phenylalanine 3.4mg per lozenge
- store at 20 - 25°C (68 - 77°F)
- keep POPPAC tightly closed and protect from light

Inactive ingredients acacia, aspartame, calcium polycarbophil, corn syrup solids, flavors, lactose, magnesium stearate, maltodextrin, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, soy protein, triethyl citrate, xanthan gum

Questions or comments? call toll-free **1-888-569-1743** (English/Spanish) weekdays (9:00 am - 4:30 pm ET)

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21330/S-013

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	5/23/2012
From	Joel Schiffenbauer, MD
Subject	Deputy Division Director Summary Review
NDA/BLA # Supplement #	NDA 21-330/S-013
Applicant Name	GlaxoSmithKline
Date of Submission	7/29/2011
PDUFA Goal Date	5/29/2012
Proprietary Name / Established (USAN) Name	Nicorette Lozenge (previously Commit)/Nicotine Polacrilex
Dosage Forms / Strength	Oral lozenge
Proposed Indication(s)	1. Smoking cessation
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Priscilla Callahan-Lyon, Jacqueline Spaulding, Celia Winchell
Statistical Review	
Pharmacology Toxicology Review	
CMC Review/OBP Review	
Microbiology Review	
Clinical Pharmacology Review	David Lee, Yun Xu
DDMAC	
DSI	
CDTL Review	Daiva Shetty
OSE/DMETS	
OSE/DDRE	
OSE/DSRCS	
Other/labeling	Mary Robinson, Colleen Rogers

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

Nicorette nicotine polacrilex lozenge, NDA 21-330, was approved for OTC marketing Oct 31, 2002. The lozenges are marketed in doses of 2 mg and 4 mg with the indication to "reduce withdrawal symptoms, including nicotine craving associated with quitting smoking." At the time of approval, GSK was granted a deferral for submission of pediatric studies for children ages 10 to 17 years and a waiver for pediatric study requirements for children under age 10 years. The applicant has now submitted information to address the pediatric studies required for the appropriate age range.

To support this supplemental application, GSK submitted the following:

- Study S1330074, a dose-escalating, pharmacokinetic evaluation of nicotine patch, gum, and lozenge formulations in adolescents 13 to 17 years of age
- Postmarketing safety data in adolescents from the GSK's worldwide clinical safety database for nicotine patch, gum, and lozenge from October 31, 2007 to October 30, 2011
- Efficacy data from the published literature, consisting of publications originating from clinical trials in adolescent smokers

This review will focus on the data presented to support the efficacy and safety of NRT in the pediatric population.

2. Background

For details of the regulatory history the reader is referred to the medical officer's review.

GSK submitted results of Study S1330074, "A Pharmacokinetic and Safety Study of (b) (4) Nicotine Replacement Therapy Formulations in Adolescent Smokers, " on August 20, 2007. This open-label, dose escalation study sought to characterize the pharmacokinetic (PK) profiles and evaluate safety of three nicotine replacement therapy formulations (patch, gum, and lozenge) in adolescent smokers aged 10 to 17. GSK intended to claim satisfactory completion of the requirements under the Pediatric Research Equity Act (PREA) with this data only. Study S1330074 was reviewed by DNCE and the Pediatric Maternal Health Staff (PMHS) and it was concluded that the findings were not adequate to satisfy PREA requirements.

On August 19, 2008, FDA notified GSK that the terms of PREA were not fulfilled. The letter

stated in part that "the pharmacokinetics study in the August 20, 2007 submission does not satisfy this commitment because it does not adequately assess the safety and efficacy of Commit in children ages 10 – 17 years."

GSK then met with FDA on February 4, 2009 to discuss the path forward to address the PREA requirements. FDA advised GSK that in order to meet PREA obligations, GSK can either conduct a de novo clinical efficacy study using the lozenge or submit full published literature reports to support their position that the required studies under PREA have been completed.

On March 25, 2011, GSK submitted an efficacy supplement containing a comprehensive review of published literature on adolescent smoking cessation. However, FDA notified GSK on May 19, 2011 that the application was unacceptable without payment of the appropriate user fee. Subsequently GSK paid the required fee on August 9, 2011 and this submission is now being reviewed.

3. CMC/Device

No new data submitted in this supplement.

4. Nonclinical Pharmacology/Toxicology

No new data submitted in this supplement.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewer provided the following:

In this submission, the Applicant submitted a comprehensive review of the published literature, including full text articles and primary data where available, as well as a brief summary of the GSK adolescent PK study, Protocol S1330074, entitled "A Pharmacokinetic and Safety Study of (b) (4) *Nicotine Replacement Therapy Formulations in Adolescent Smokers." It is noted that Study S1330074 was submitted to N 21330 in 8/20/07. From a clinical pharmacology perspective, Study report S1330074 was reviewed.*

Recommendation
The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCPII) has reviewed the information submitted in the current application. From clinical pharmacology perspective, the submitted information in this supplement is acceptable. Due to the recruitment difficulties, no 10 – 12 year olds subjects participated in Study S1330074. The nicotine pharmacokinetic data submitted in pediatric patients 13-17 years are acceptable (Study S1330074). Comparing the historical adult nicotine pharmacokinetic parameters and the pediatric (13-17 years old) nicotine pharmacokinetic

parameters presented in this submission, the nicotine pharmacokinetic parameters were comparable.

I agree with the clinical pharmacology assessment. The study appears adequate to determine that the PK characteristics of NRT in the pediatric population studied are comparable to adults.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Clinical data presented in this supplemental application includes the following:

1) Study S1330074, a dose-escalating, pharmacokinetic evaluation of nicotine patch, gum, and lozenge formulations in 45 adolescents 13 to 17 years of age
2) GSK's worldwide clinical safety database for nicotine patch, gum, and lozenge from October 31, 2007 to October 30, 2011
3) Literature provided by the applicant, consisting of eight publications originating from seven clinical trials in adolescent smokers

There have been a number of studies on the use of NRT in adolescent smoking cessation. The applicant has included eight publications summarizing seven randomized, double-blind, controlled studies (six placebo-controlled, one active-controlled). Other published reports, including two randomized, open-label, controlled trials and two uncontrolled trials were also included and were not reviewed for efficacy. The five published reports and one clinical pharmacology trial reviewed for efficacy and safety are shown in the Table below.

Study	Design	N	Duration of treatment	Age (years)	Treatment	Other interventions
GSK S1330074	Pharmacokinetic study: two-period, dose-escalation	Period 1: 45	Single-dose	13-17	Lozenge 2 mg Patch 14 mg Gum 2 mg	None
		Period 2: 37	Single-dose		Lozenge 4 mg Patch 21 mg Gum 4 mg	
Roddy 2006	Published report; R, DB, PC study	98	6 weeks	12-20	Patch Placebo	Behavioral counseling
Moolchan 2005	Published report; R, DB, PC	120	12 weeks	13-17	Patch Gum Placebo	Cognitive behavioral therapy
Wold 2005	Public Presentation; R, DB, PC	50	10 weeks	13-18	Patch Placebo	Not Reported
Stotts 2003	Published Report; R, DB, PC	303	6 weeks	14-19	Patch Placebo Usual care	Group Behavioral intervention classes vs. 5-10 minute counseling and f/u phone call
Hanson 2003	Published Report: R, DB, PC	100	10 weeks	13-19	Patch Placebo	Cognitive behavioral therapy

Efficacy of Nicorette lozenge in the adult population was previously established in the pivotal placebo controlled, efficacy and safety trial (S1410043) involving 1818 subjects in the original application to NDA 21-330. A complete review of efficacy was previously conducted by the Division of Anesthetic, Analgesic, and Addiction Products (DAAAP). The reader is referred to the review by Drs. Spaulding and Winchell for details of each trial, and also to the review by Drs. Callahan-Lyon and Shetty.

In summary, while the literature reports submitted do not clearly support the applicant's conclusion that NRTs are ineffective smoking cessation treatment for the adolescent population, the reports identify some difficulties associated with conducting adequate and well-controlled trials that would address the issue of efficacy in adolescents:

1) Difficulty recruiting: While most of the studies, including the PK study GSK conducted, attempted to recruit younger subjects, most participants were ages 14 or older. Enrolling younger adolescents for these studies appears to be difficult and there may be several reasons including adolescents are not really addicted; obtaining parental consent is challenging for this age group and parents may not be aware that their child is smoking.

2) High drop-out rate: Even when the investigators were successful in recruiting subjects, the drop-out rates were very high – usually > 50%. There were several different approaches used to try to address this issue (run in period, confirming motivation to quit with a questionnaire, end of study payment etc) but with apparently limited success.

3) Difficulties of Study Design/Compliance: This is particularly challenging for NRT products that are meant for 'as needed' use. Most of the adolescent subjects are students and administering a medication to a student on an 'as needed' basis is very difficult. The reports included in this application were primarily studies conducted using the nicotine patch which

is only applied once a day and circumvents this challenge. None of the literature reports submitted included a trial of nicotine lozenges.

Drs. Spaulding and Winchell conclude that based on the data provided, adequate and well-controlled studies in smokers less than 18 years are highly impractical for the following reasons:

- *Although surveys suggest that approximately 5 million high school and middle school students are considered "smokers," meaning they report having smoked on 1-2 days in the past month, a considerable fraction of these smokers are over the pediatric age range generally considered under PREA. Moreover, only about half are likely to be regular smokers, and of these, only a subset would be considered appropriate candidates for nicotine replacement therapy.*
- *The population available to enroll in a trial of NRT would need to meet the following criteria:*
    - *Patients must have established addiction (Some occasional smokers may not be nicotine-dependent.)*
    - *Patients should have a history of quit attempts (to establish that they are addicted and motivated to quit)*
    - *Patients must be willing to quit and interested in seeking treatment to help them quit.*
    - *Patients must agree to participate in a clinical trial*
    - *Parents must agree and sign an informed consent*
    - *Patients must have ability to carry the product to school and use it as needed. This product, a lozenge intended for p.r.n. use, is not suited to use in schools that have restrictions on self-administration of medication.*

In summary, both DNCE and DAAAP came to the same recommendation that the sponsor should be granted a waiver for the PMR in children less than 18 years of age. The PeRC agreed with this recommendation (see below).

In conclusion, because of the limitations of the studies, the data included in this submission does not support efficacy of NRTs for smoking cessation in the adolescent population, but also does not demonstrate that there is no efficacy. This will be reflected in the labeling comments (see below).

8. Safety

The available safety data show no evidence of a safety concern for the use of NRT products in the adolescent population. The PK study (S1330074) is the only study included in this application in which the nicotine lozenge was administered. The most common adverse events reported were nausea, pharyngitis, eructation and anemia (anemia was only reported for this small PK study and likely of no significance). There were no serious adverse events.

The other reports in this submission are from published literature studies. The NRTs administered in these studies were the nicotine patch (ten reports), nicotine gum (two reports),

and nicotine nasal spray (one report). The general pattern of adverse events was similar to the known results from studies in adults. No new safety issues were identified and there was no evidence of any significant safety concerns specifically associated with administration of NRT products to adolescents. The review of the worldwide pharmacovigilance data does not raise any new safety issues.

The applicant concludes "NRT has been shown to be well tolerated in adolescent populations and has a similar PK profile to that of adults."

I agree that this data does not raise any new safety concerns.

9. Advisory Committee Meeting

No advisory committee meeting was determined to be required for this supplement addressing PREA.

10. Pediatrics

The PeRC members agreed with the divisions' conclusions that efficacy studies for nicotine cessation using nicotine lozenge in adolescents are highly impractical to conduct because of the conditions of use, and agreed with the plan to release the sponsor from the current PMR, and convert the current pediatric requirement to a full waiver. PeRC also agreed with additional changes to the label to address the conclusions of the reviewers.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

The only change proposed by the applicant from current Drug Facts labeling includes the following statement under ***Directions***:

"If you are under 18 years of age, ask a doctor before use. (b) (4) (b) (4)"

Based on her assessment of the data provided, Dr. Callahn-Lyon did not agree with the applicant's wording and provided the following comments:

At this time, the recommendation is for the statement to be revised to:

"If you are under 18 years of age, ask a doctor before use; (b) (4) (b) (4) *."*

However, a more consumer "friendly" wording would be "No studies have been done to show if this product will work for you."

This revised wording appears acceptable, and was discussed with the review team.

13. Decision/Action/Risk Benefit Assessment

This application from GlaxoSmithKline (GSK) was submitted to address the requirement to evaluate the efficacy and safety of nicotine polacrilex lozenges in the pediatric population ages 10 to 17 years.

To address safety, GSK included data from their pharmacokinetic study conducted on subjects ages 13 to 17 years, data from several published literature reports of studies conducted on adolescent populations using other NRT products, and a review of the GSK post-marketing data for all reports for patients < 18 years of age involving nicotine drug products for a three year period. I agree with the MO review that no new safety signals were identified.

To address efficacy, GlaxoSmithKline examined data from the published literature. None of these studies provide convincing evidence for the efficacy of NRT in the adolescent population because of limitations in the study conduct and design.

Based on their evaluation, GSK proposes changes to the product labeling regarding the lack of efficacy in those < 18 years of age. The sponsor believes the data submitted and the proposed labeling change should release them from obligations for additional pediatric study of this product.

Based on the submission, the question before us is whether the applicant has provided sufficient information to address the PREA requirement to study the use of nicotine lozenge in the appropriate pediatric population and whether to release them from the requirement to perform additional studies. There are clearly aspects of these types of studies in this population for a product that is to be used on an "as needed" basis, that make them difficult to perform (as discussed previously). For this product, these studies may indeed be highly impractical. I agree with the PeRC recommendation to waive the requirement for additional studies and release the applicant from their PREA requirements. However, I would not support a waiver for studies for all NRT products in this population, as it may be possible to study other products with different use patterns (such as a patch or once a day oral medication) that would make these studies in adolescents more feasible. I believe that additional approaches can be taken to address the issues of drop-outs or recruitment difficulties, for example longer run-in periods to ensure that adolescents are motivated to quit, to warrant additional attempts at such trials in the future, for products that may have different modes of action. It is worth pursuing this since it is agreed that smoking in adolescents is a public health issue and that many adult

smokers begin their habit of lifelong smoking as younger adults. Given adequate resources and efforts, I believe that information obtained from studies already performed can be used to design trials with a greater chance of success. Indeed, the authors of a number of the papers cited above suggest that additional studies are needed. Furthermore, at this time the division that oversees prescription drugs for smoking cessation has determined that pediatric studies should be performed for those therapies. I do not favor waiving studies in this population for all NRT's.

Therefore, I recommend that the applicant receive an approval for the labeling changes and a release from PREA required studies for NDA 21-330 based on the impracticality of the studies for this product in the adolescent population.

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

/s/

JOEL SCHIFFENBAUER
05/23/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21330/S-013

OFFICER/EMPLOYEE LIST

Officer/Employee List
Supplemental New Drug Application:
021330/S-013

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified:

Celia Winchell
Jackie Spaulding
David Lee
Yun Xu
Priscilla Callahan-Lyon
Joel Schiffenbauer

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21330/S-013

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 4, 2012
From	Daiva Shetty, MD
Subject	Cross-Discipline Team Leader Review
NDA# **Supplement#**	21-330 S-013
Applicant	GlaxoSmithKline Consumer Healthcare (GSK)
Date of Submission	July 29, 2011
PDUFA Goal Date	May 29, 2012
Proprietary Name / Established (USAN) names	Nicorette® (formerly called Commit®) / nicotine polacrilex
Dosage forms / Strength	Lozenge, 2mg and 4 mg
Proposed Indication(s)	Reduce withdrawal symptoms nicotine craving, associated with quitting smoking, including
Recommended:	Approval

1. Introduction

This supplemental NDA is submitted to fulfill the pediatric post-marketing commitment as required by the Pediatric Research and Equity Act (PREA). Based on the data submitted, the sponsor is requesting the following labeling: "If you are under 18 years of age, ask a doctor before use. (b) (4)"

To support this supplemental application, GSK submitted the following:

- Study S1330074, a dose-escalating, pharmacokinetic evaluation of nicotine patch, gum, and lozenge formulations in adolescents 13 to 17 years of age
- Postmarketing safety data in adolescents from the GSK's worldwide clinical safety database for nicotine patch, gum, and lozenge from October 31, 2007 to October 30, 2011
- Efficacy data from the published literature, consisting of publications originating from clinical trials in adolescent smokers

2. Background

NDA 21-330 was initially approved on October 31, 2002. It provided for nicotine polacrilex lozenge (Commit® nicotine lozenge) to be marketed as an over-the-counter product. Nicotine polacrilex (2 mg and 4 mg) is a nicotine replacement product intended for use as an aid to smoking cessation by reducing withdrawal symptoms.

This application has a rather complicated regulatory history. In December 2000, the Association of American Physicians and Surgeons, Competitive Enterprise Institute and Consumer Alert jointly filed suit to challenge the Agency's authority in enforcing the Pediatric Rule. On October 17, 2002, the U.S. District Court for the District of Columbia ruled against

FDA. At the time of approval for NDA 21-330, the Agency had not decided whether to appeal this ruling or to ask for a stay of the court's order.

The approval letter informed GSK that pediatric studies would be required if the Pediatric Rule remained in effect and/or were upheld on appeal. The letter stated that FDA would notify GSK whether NDA 21-330 would be subject to the requirements of the Pediatric Rule, pending resolution of the lawsuit. Were the Pediatric Rule to remain in effect, the approval letter granted deferral of submission of pediatric studies for patients 10-17 years until October 31, 2007. The approval letter waived pediatric study requirement for patients under age 10. However, it appears that FDA did not explicitly notify GSK of the final outcome of the lawsuit or confirm with GSK that the Pediatric Rule remained in effect. FDA also did not specify what kind of studies would be required under the PMR. One meeting was held between FDA and GSK in 2009 to discuss the data requirements. At this meeting FDA provided two options to GSK: to conduct a de novo efficacy study or to provide data from medical literature.

For more details on the regulatory history of this supplemental application, see Dr. Priscilla Callahan-Lyon's review.

3. CMC/Device

Not applicable.

4. Nonclinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology/Biopharmaceutics

GSK submitted results of one pharmacokinetic (PK) Study S1330074, "A Pharmacokinetic and Safety Study of (b) (4) Nicotine Replacement Therapy Formulations in Adolescent Smokers," which has been reviewed in detail by Dr. David Lee. See his review entered in DARRTS on 3/26/12. Safety data gathered during this study has been reviewed by Dr. Callahan-Lyon (see her review entered in DARRTS on 4/11/12).

This open-label, dose escalation study sought to characterize the PK profiles and evaluate safety of three nicotine replacement therapy formulations (patch 14 and 21 mg, gum 2 and 4mg, and lozenge 2 and 4 mg) in adolescent smokers aged 10 to 17. However, because of the difficulty in finding young smokers, the subjects recruited for the younger smoker group were either 13 or 14 years old; only five subjects were 13 years of age (4 females and 1 male). A total of 45 subjects (21 males and 24 females) aged 13 to 17 years were enrolled and completed session 1. A total of 37 subjects completed session 2. Summary of the PK results in adolescents is presented in Table 1 below:

Table 1. Summary of the nicotine PK parameters in adolescents (Study S1330074)

Product		T_{max} (hr)	C_{max} (ng/ml)	$AUC0_{-\infty}$ (ng*hr/ml)
Patch	14 mg	5.0	16.4	227.6
	21 mg	4.6	24.3	327.8
Lozenge	2 mg	1.1	5.4	21.4
	4 mg	1.2	11.1	44.5
Gum	2 mg	0.6	6.2	19.7
	4 mg	0.7	10.8	34.9

The above parameters were compared to those in adults. The adult pharmacokinetics parameters were obtained from PK/safety review of NDA 21-330 resubmission by Dr. Jin Chen, dated September 3, 2002. See Table 2 below.

Table 2. Summary of adult PK profiles by NRT products

Product		T_{max} (hr)	C_{max} (ng/ml)	$AUC0_{-\infty}$ (ng*hr/ml)
Patch	21 mg	10.0	17.6	290
Lozenge	4 mg	1.1	10.8	44.00
Gum	2 mg	0.8	3.3	3.675
	4 mg	0.875	7.7	8.105

Even though this is an across the study comparison, the systemic exposure of nicotine in adults and 13-17 year old pediatric subjects is generally comparable for the patch and lozenge formulations at same doses. However, the systemic exposure of nicotine from the gum formulation seems to be higher in adolescents.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

For a full review and discussion on efficacy, please refer to the clinical review from the Division of Analgesia, Anesthesia, and Addiction products (DAAAP) by Dr. Jacqueline Spaulding (entered in DARRTS on 4/4/12).

There are no controlled clinical efficacy trials evaluating the nicotine lozenge in adolescents. The FDA requested the sponsor to provide efficacy data in adolescents either by conducting a de novo clinical efficacy study using the lozenge or by providing data from medical literature. The sponsor chose to rely on the published literature and submitted 12 full-text publications that evaluated the use of NRT (mainly nicotine patch therapy) in adolescent smoking cessation. Since some of the publications did not have primary efficacy analyses or did not assess quit rates, the reviewer chose to review only five randomized, double-blind, placebo-controlled studies and summarized discussion of two randomized, double-placebo, controlled

studies. My review will provide short summaries of findings from the reviewed articles. For details please refer to the primary review.

1. Roddy E, Romilly N, Challenger A, Lewis S, Britton J. Use of nicotine replacement therapy in socioeconomically deprived young smokers: a community based pilot randomized controlled trial. Tob Control, 5/2006, (15) 373-376.

This was a randomized, double-blind, placebo-controlled 6-weeks duration study in socioeconomically disadvantaged young smokers (ages 12-20 inclusive). It compared Nicotine patch (15 mg/10 mg/5 mg) for 2 weeks each vs. Placebo patch.

A total of 145 participants volunteered for screening and 98 were deemed eligible for participation in the study. Only 8.2% (8 /98) of study participants completed the study with 37% (N=3/8) of subjects receiving active treatment as compared to 63% (N=5/8) of subjects receiving placebo treatment. A small percentage of study participants (2.0%) withdrew from the study secondary to an adverse event; with similar rates in both active and placebo treatment groups (50% respectively). At four weeks, five subjects receiving active NRT and two receiving placebo were abstinent, and at 13 weeks no subjects in either the active or placebo treatment groups were reported to be abstinent.

2. Moolchan ET, Robinson ML, Ernst M, Cadt JL, Pickworth WB, Heishman SJ. Safety and Efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. Pediatrics, 4/2005, (115) 407-414.

This was a 12 week duration randomized, double-blind, double-dummy, 3-arm trial in 120 adolescent smokers (13 to 17 years of age, inclusive). Study Treatments consisted of: 1) Nicoderm (nicotine patch 21 and 14 mg) and Placebo gum, 2) Nicorette (nicotine gum 2 and 4 mg) and Placebo patch, and 3) Placebo patch and Placebo gum.

Of the 120 participants randomized to receive treatment 44% (53/120) completed the study. The proportion of randomized participants who completed the study were 52.9% (18/34) for the nicotine patch group, 41.3 % (19/46) for the nicotine gum group, and 40% (16/40) for the placebo patch group.

The proportion of each treatment group that achieved abstinence was as follows: nicotine patch group (17.7%, N=6/34); nicotine gum group (6.5%, N=3/46); and the placebo group (2.5%, N=1/40) with differences between the nicotine patch and placebo demonstrating statistical significance (p=0.043).

3. Wold AL, Whitmore EA, Gianani EJ, Mikulich-Gilbertson SK. Nicotine Patch Therapy for Adolescent Smokers: A Pilot Study. 2005, Presented at: College on Problems of Drug Dependence Conference

This was a randomized, double-blind, placebo-controlled pilot study in adolescents ages 13-19 in a standard day treatment program for serious conduct and/or substance use problems. A

total of 50 subjects were enrolled into two treatment arms: Nicotine patch and Placebo patch. Study lasted 10 weeks (double-blind treatment).

Sixty-eight (68%) percent (34/50) of study participants completed the 10-week randomized treatment and 78% (39/50) of participants completed the one month follow up assessment.

A total of 8% (4% in each treatment group) reported smoking abstinence during the study. Overall, 72% of participants in the nicotine patch group compared to 48% of the placebo patch group reported >80% reduction of daily cigarette use during their time on treatment. For those participants who completed the 10-week study, those in the nicotine patch group reported reduction of their smoking significantly more than those in the placebo group (reduction of 15 cigarettes per day (CPD) versus 8 CPD respectively, p=0.02).

The results of this study show that while the overall compliance rate for the study was adequate (68%), only 8 % (N=4) of study participants achieved abstinence during the study treatment period.

4. Hanson K, Allen S, Jensen S, Hatsukami D. Treatment of adolescent smokers with the nicotine patch, Nicotine Tob Res, 4/2003, (5) 515-526.

This was a randomized, double-blind, placebo-controlled pilot study in 100 adolescents ages 13-19 in a standard day treatment program for serious conduct and/or substance use problems The study duration was 13 weeks (10 weeks double-blind treatment). Study arms consisted of Nicotine and Placebo patches in conjunction with intensive cognitive-behavioral therapy and a contingency management program.

A total of 100 adolescents started the study with 53% (N=53) reported to have completed treatment. Follow-up rates among the 53 treatment completers were 49% at 14 weeks and 38% at 36 weeks.

Reported results showed that the nicotine patch group had a statistically significant lower craving score compared to the placebo patch group (p=0.011) and a lower overall mean withdrawal symptom score (p=0.025) at 2 weeks post-quit. However, results also showed no difference between nicotine patch and placebo in helping adolescents to quit smoking.

5. Stott RC, Roberson PK, Hanna EY, Jones SK, Smith CK. A randomized clinical trial of nicotine patches for treatment of spit tobacco addiction among adolescents. Tobacco Control 2003;12:iv11-iv15.

This was a randomized, double-blind, placebo-controlled study in 303 adolescent males, ages 14-19 with regular use of spit tobacco (ST) for previous year. Duration of the study was 6 weeks (follow-up through 1 year). Study treatments consisted of three arms:

1. Nicotine patch
    - Light to moderate users (<150 ng/ml in baseline saliva sample) 14 mg x 3 weeks followed by 7 mg x 3 weeks

- Heavy users (≥150 ng/ml in baseline saliva sample) 21 mg x 2 weeks, 14 mg x 2 weeks, and 7 mg x 2 weeks

2. Placebo patch
3. Usual Care – 10 minute counseling with follow-up call in 2 weeks

In conjunction with group behavioral intervention classes

A total of 98 out of 303 study participants that were originally enrolled completed the study: 25 in the usual care treatment group, 33 in the nicotine patch treatment group and 40 in the placebo patch treatment group; 130 remained in the study for 1 year.

There was no significant difference in the ST abstinence rate between the nicotine and placebo patch groups at 9 weeks (31.6% vs. 29% respectively); 6 months (15.3% vs. 17.0% respectively), and 1 year (17.3% vs. 25.0% respectively). With respect to the cigarette abstinence at 1 year, the placebo group had a higher percentage of participants reporting abstinence compared to the nicotine patch group (23.0% vs. 12.2% respectively).

The results of the study show that use of the nicotine patch does not provide improvement over placebo patch when attempting to quit ST, snuff, chew tobacco, and cigarettes.

6. Franken FH, Pickworth WB, Epstein DH, Moolchan ET. Smoking Rates and Topograph Predict Adolescent Smoking Cessation Following Treatment with Nicotine Replacement Therapy. Cancer Epidemiology, Biomarkers & Prevention 2006;15(1): 154-157.

This was a 12-week randomized, double-blind, double-dummy, 3-arm trial in 99 adolescent smokers (13 to 17 years of age, inclusive). The treatment arms consisted of:
1. Nicoderm (nicotine patch 21 and 14 mg) and Placebo gum
2. Nicorette [nicotine gum 2 and 4 mg) and Placebo patch
3. Placebo patch and Placebo gum

At the end of the 3 month treatment period, 12% of participants were reported to have achieve prolonged abstinence, at the 3 month follow-up, 15% were point prevalent abstinence. End of treatment (12 weeks) abstinence was predicted by baseline CPD and by puff volume. At the 3-month post treatment follow-up visit abstinence was reportedly significantly associated with puff volume.

This study was not designed to recruit tobacco-addicted adolescent, nor was it designed to evaluate efficacy of NRT. The study attempted to predict the reliability of exposure variables such as CPD and smoking topography measures of adolescent smoking cessation and by proxy degree of tobacco dependence. Study results appear to show that markers of the frequency and intensity of smoke exposure such as CPD and smoking-topography measure may be useful predictors of adolescent smoking cessation, and by proxy, degree of tobacco dependence.

7. Killen JD, Ammerman S, Rojas N, Varady J, Haydel F, Robinson TN. Do Adolescent Smokers Experience Withdrawal Effects When Deprived of Nicotine? Experimental and Clinical Psychopharmacology 2001, Volume 9, No 2: 176-182

This was a randomized, double-blind, placebo-controlled study in 105 adolescent smokers, ages 13-18 from homeless shelter and alternative high schools. The study consisted of two 1-8 hour treatment sessions: nicotine patch (15 mg) and Placebo patch.

Overall, the study suggests that adolescent smokers exhibit signs and symptoms associated with abrupt withdrawal of nicotine; no meaningful differences were noted between NRT and placebo when treating these nicotine withdrawal symptoms.

Conclusion:
Of the seven randomized, double-blind, placebo controlled studies, six publications summarized five randomized, double-blind, placebo-controlled studies that specifically addressed the efficacy of NRT for smoking cessation in adolescents. Of note, none of these five studies were conducted with the Commit lozenge (2 or 4 mg).

Studies enrolled populations primarily older than the targeted pediatric age ranges mentioned in the PREA-related correspondence to GSK, and most used transdermal nicotine, rather than the a self-titrated dosage form similar to the lozenge. As noted above, none used the lozenge. None of the reported studies showed that NRT is efficacious in adolescents. However, "the lack of demonstrated efficacy of NRT in adolescents" may not necessarily be a result of ineffective drug treatment but rather due to other contributing factors such as poor study design, low enrollment rates, high dropout rates, and small sample sizes.

DAAAP's conclusion on the published studies is - adequate and well-controlled studies in smokers less than 18 years are highly impractical for the following reasons:

- Although surveys suggest that approximately 5 million high school and middle school students are considered "smokers," meaning they report having smoked on 1-2 days in the past month, a considerable fraction of these smokers are over the pediatric age range generally considered under PREA. Moreover, only about half are likely to be regular smokers, and of these, only a subset would be considered appropriate candidates for nicotine replacement therapy.
- The population available to enroll in a trial of NRT would need to meet the following criteria:
    - Patients must have established addiction (Some occasional smokers may not be nicotine-dependent.)
    - Patients should have a history of quit attempts (to establish that they are addicted and motivated to quit)
    - Patients must be willing to quit and interested in seeking treatment to help them quit.
    - Patients must agree to participate in a clinical trial
    - Parents must agree and sign an informed consent
    - Patients must have ability to carry the product to school and use it as needed. This product, a lozenge intended for p.r.n. use, is not suited to use in schools that have restrictions on self-administration of medication.

Both divisions – DNCE and DAAAP – came to the same recommendation: the sponsor should be granted a waiver for the PMR to conduct a study for smoking cessation with the nicotine lozenge in children less than 18 years of age, and the Pediatric Review Committee (PeRC) agreed.

I agree with this recommendation.

8. Safety

For a full review and discussion on safety, please refer to the clinical review by Dr. Priscilla Callahan-Lyon (entered in DARRTS on 4/11/12).

Safety data to support this application comes from three different sources:

1. PK study S1330074
2. Medical literature
3. GSK's worldwide clinical safety database for nicotine patch, gum, and lozenge from October 31, 2007 to October 30, 2011. The search focused on adolescents younger than 18 years of age

Summary of safety data from the PK study

The only clinical study evaluating safety of the nicotine lozenge in adolescents submitted by GSK was the PK Study S1330074. Safety population consisted of a total of 45 subjects (21 males and 24 females) aged 13 to 17 years who completed session 1 and 37 subjects who completed session 2. A total of 61 adverse events (AEs) were reported by 30 (67%) of the 45 subjects dosed during session one (lower doses of each formulation). A total of 58 adverse events (AEs) were reported by 27 (69%) of the 39 subjects dosed during session two (higher doses of each formulation). The most commonly reported AEs were nausea, pharyngitis, eructation and anemia; only nausea, pharyngitis and eructation were deemed by the investigator to be treatment-related adverse events. All but one of the reported AEs were considered by the investigator to be mild or moderate in intensity; the only AE that was classified as severe was "throat burn" (Nicorette 4 mg gum group). Two subjects were discontinued due to adverse events. They both reported nausea and vomiting, which were considered to have a highly probable relationship to the study medication.

Summary of safety data from the medical literature

The sponsor submitted a total of 11 publications reporting data from controlled and uncontrolled clinical trials in adolescent smokers. Nicotine replacement therapies (NRTs) administered in these trials were the nicotine patches or nicotine gum. None of the published articles had data on the use of the nicotine lozenge in adolescents. Cutaneous reactions and headaches were the most common complaints, but overall, the general pattern of adverse events was similar to the known results from studies in adults. There was no evidence of any significant safety concerns specifically associated with administration of NRT products to adolescents.

The most commonly reported adverse event related to NRT (specifically patch therapy) included: itching, redness and erythema at the patch site. Other notable adverse reactions included pain, burning, and headache.

Summary of safety data from the GSK's postmarketting database
GSK's database was searched for AEs related to nicotine patch, lozenge, or gum use in less than 18 years of age, between 10/31/07 to 10/26/11. A total of 68 reports were retrieved. Two of the reports documented the use of nicotine patch and gum or lozenge; these two reports are presented in both the nicotine patch and oral formulations groups. Table 3 below summarizes all reports.

Table 3. Summary of GSK Postmarketing Reports for Consumers <18 years old

Reports	Nicotine patch	Oral formulations of nicotine	
		Gum	Lozenge
Serious[1] and non-serious	40	16	14
Serious	3	4	2
Healthcare professional as report source	3	1	2
Healthcare professional as report source and serious	0	0	0
US reports	16	9	6

[1] Serious report: a report where at least one of the adverse events is serious.

Most of the reports of adverse events in children (< 12 years of age) were due to accidental exposure to single doses of nicotine. In several cases (n=7), there were no associated symptoms related to the nicotine exposure and the majority of the reported events were gastrointestinal complaints (nausea and vomiting) or neurological events (tremor or dizziness). Most of the adverse event reports in adolescents (12 to 17 years of age) were non-serious and many included events known to be associated with nicotine products.

The overall conclusion by the clinical reviewer is that the safety profile of the nicotine products in adolescent population is consistent with that of adults and does not raise any new safety issues. I agree with this assessment. There are no notable outstanding safety issues.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

This pediatric assessment was presented to the Pediatric Review Committee (PeRC) at the meeting held on May 2, 2012.

The PeRC members agreed with the divisions' conclusions that efficacy studies for nicotine cessation using nicotine lozenge in adolescents are difficult to conduct because of the conditions of use and agreed with the plan to release the sponsor from the current PMR and convert the current pediatric requirement to a full waiver. PeRC thought that the main reason for which the studies cannot be conducted is the inability for patients to carry the product to school and use it as needed. This product, a lozenge intended for p.r.n. use, is not suited to use in schools that have restrictions on self-administration of medication. PeRC also agreed with the divisions' proposed labeling, i.e. "If you are under 18 years of age, ask a doctor before use; (b) (4)" Labeling revisions were later discussed at the team's labeling meeting on May 3, 2012. The team came to a conclusion that the most appropriate language would be: "if you are under 18 years of age, ask a doctor before use. No studies have been done to show this product will work for you."

11. Other Relevant Regulatory Issues

There are no other outstanding regulatory issues.

12. Labeling

For complete review of the proposed label, please refer to the labeling review by Mary Robinson, entered in DARRTS on 4/11/12. In her review, she made one recommendation: For the 189-count club pack, revise the net quantity statements on the PDP (both top and bottom) for consistency with 21 CFR 201.62 and other Nicorette packaging as follows:
"189 Lozenges
2 mg/4 mg Each
(7 Poppac Containers of 27)"
This labeling change should be communicated to the sponsor prior to the regulatory action date.

Under PREA, data gathered during pediatric from the pediatric assessment, has to be reflected in the product's labeling. GSK proposes to revise the "Directions" section of the Drug Facts label by adding the following:
"If you are under 18 years of age, ask a doctor before use. (b) (4) (b) (4)"

As discussed at the team's labeling meeting, the label will read:
"if you are under 18 years of age, ask a doctor before use. No studies have been done to show this product will work for you."

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Clinical teams differed in their recommendations on the regulatory action for this supplement. DNCE recommended Approval, and DAAAP recommended Complete Response.

In my opinion, this application should be APPROVED because the sponsor fulfilled their commitment by providing data in adolescents and we are changing the approved label based on the submitted information. Even though efficacy was not demonstrated, we learned from the data that there are no new safety issues and that the systemic exposure to nicotine from NRTs in adolescents is similar to that of adults. Because studies with this nicotine formulation are difficult to conduct, the sponsor should be granted a full waiver of the requirement to conduct pediatric studies for this particular drug product because "necessary studies are impossible or highly impracticable."

I recommend an Approval regulatory action.

- Risk Benefit Assessment

In general, based on the data submitted, nicotine lozenge is safe in adolescents. Since the conditions of use to demonstrate efficacy cannot be met for this population, efficacy has not been established.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Not applicable.

- Recommendation for other Postmarketing Requirements and Commitments

Not applicable.

- Recommended Comments to Applicant

Labeling revisions specified in the labeling section of this review have been conveyed to the sponsor. If the sponsor revises the label as requested, there are no other recommendations to the sponsor.

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/s/

DAIVA SHETTY
05/05/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21330/S-013

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA – Efficacy Supplement
Application Number(s)	21330
Priority or Standard	Standard
Submit Date(s)	08/09/11
Received Date(s)	08/09/11
PDUFA Goal Date	
Division / Office	Division of Anesthesia, Analgesia and Addiction Products
Reviewer Name(s)	Jacqueline A. Spaulding MD
Review Completion Date	04/04/12
Established Name	Commit™
(Proposed) Trade Name	Nicotine polacrilex
Therapeutic Class	Nicotine replacement
Applicant	GlaxoSmithKline (GSK)
Formulation(s)	2 and 4 mg lozenges
Dosing Regimen	Weeks 1 to 6: 1 lozenge every 1 to 2 hours Weeks 7 to 9: 1 lozenge every 2 to 4 hours Weeks 10 to 12: 1 lozenge every 4 to 8 hours
Indication(s)	Aid in smoking cessation
Intended Population(s)	Adult & Pediatric

Template Version: March 6, 2009

Appears this way on original.

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend a complete response action for this efficacy supplemental application which proposes to include additional language regarding the lack of effectiveness of Commit (nicotine polacrilex) lozenges 2 and 4 mg in adolescents. This supplement was intended to fulfill a Postmarketing Requirement (PMR) under the Pediatric Research Equity Act (PREA)[1] that was communicated to the Applicant by the Division of Nonprescription Clinical Evaluation (DNCE) on 08/19/08.,

In this submission, Glaxo SmithKline (GSK) seeks to make the case that efficacy studies required under PREA do not need to be conducted because there is evidence to demonstrate that their product is ineffective in the pediatric population.

Based on my review of efficacy information submitted in the application; the sponsor has not provided adequate evidence to demonstrate lack of efficacy of nicotine replacement therapy (NRT), or, more specifically, of Commit Lozenge, in adolescents. The supplemental application contains data from twelve full-text publications that evaluated the use of NRT (mainly nicotine patch therapy) in adolescent smoking cessation including:

- Seven randomized, double-blind, placebo-controlled studies
- One active-controlled study
- Two randomized-open-label, controlled studies and
- Two uncontrolled studies

[1] GSK was informed that, under the provisions of PREA, they would be required to study safety and efficacy of Commit Lozenge in children ages 10-17. This age range was patterned after a Pediatric Written Request (PWR) sent to SmithKline Beecham (predecessor to GSK) for Nicorette Gum and Nicoderm transdermal system in 1998. It should be noted that this PWR was sent pursuant to provisions of the Best Pharmaceuticals for Children Act (BPCA) and prior to the passage of PREA; the age ranges cited do not completely correspond to those which are generally included under the “pediatric” definition under PREA, which does not include 17 year-olds. In this PWR, the Agency took the position that efficacy could not be extrapolated from adult studies because of unanswered questions about the way adolescent patients become addicted to tobacco.

Of the seven randomized, double-blind, placebo controlled studies, six publications summarize five randomized, double-blind, placebo-controlled studies that specifically address the efficacy of NRT for smoking cessation in adolescents. Of note, none of these five studies were conducted with the Commit lozenge (2 or 4 mg).

The sponsor believes that available evidence from randomized controlled trials does not support efficacy of NRT for smoking cessation in the adolescent population. However, "the lack of demonstrated efficacy of NRT in adolescents" may not necessarily be a result of ineffective drug treatment but other contributing factors. These factors include: poor study design, low enrollment rates, high dropout rates, and small sample sizes, Several studies enrolled a population that was primarily older than the targeted pediatric age ranges mentioned in the PREA-related correspondence to GSK, and most used transdermal nicotine, rather than the a self-titrated dosage form similar to the lozenge. As noted above, none used the lozenge. Thus, these studies, while failing to show an effect of the study drug, do not constitute a demonstration of lack of efficacy for nicotine lozenge as an aid to smoking cessation in adolescent smokers.

The safety of Commit lozenges has been demonstrated in adults. Safety information from five randomized, double-blind placebo-controlled studies evaluating efficacy of NRT shows that NRT is generally well-tolerated in older adolescent smokers. The most commonly reported adverse event related to NRT (specifically patch therapy) included: itching, redness and erythema at the patch site. Other notable adverse reactions included pain, burning, and headache.

The assessment of postmarket safety was conducted by the DNCE. At the writing of this review, DNCE staff had not reported any new or unexpected safety signals from postmarket use of NRT. Please refer to the DNCE final review for specific details regarding postmarket safety.

According to 21 CFR 201.57(f) (9) the pediatric population includes those patients aged "birth to 16 years of age." The Pediatric Written Request sent to the Sponsor for their Nicorette Gum and Nicoderm Transdermal System NDAs noted a need for studies in ages 10-17, and this age range was reiterated in the correspondence sent to GSK regarding the PREA-required studies for this application. A major limitation of the submitted information is that the majority of studies evaluating the efficacy of NRT included older adolescent smokers (>16 years of age). Thus, the information about efficacy and safety regarding NRT in these studies may not be generalizable and clinically meaningful to the full age range mentioned in the correspondence or required under PREA. The PWR noted that it was not possible to extrapolate from adult studies because of unanswered questions about the nature of tobacco addiction and the motivations for smoking and quitting in pediatric patients.

There is a paucity of smoking cessation data available on the adolescent population and the existing literature suggests that additional research should be done to better understand the utility of NRT for smoking cessation in adolescents. However, significant barriers to accomplishing this research are apparent when reviewing the submitted publications. While each study purported to study adolescent smokers, few actually enrolled or even recruited from the full range of pediatric patients to be addressed under PREA requirements.

While several of the submitted studies were open to younger patients, few were enrolled, and several studies were unable to meet their pre-specified enrollment targets, even including the older adolescent patients who are not in the CFR-defined pediatric population. Only one study was open to patients under age 13. None were open to patients under age 12.

Recent surveys reported in the most recent Report of the Surgeon General on Preventing Youth Tobacco Use[2] indicate that nearly 20% of students in 9th-12th grades and just over 5% of students in 6th-8th grades indicate that they smoked at least one or two days in the past 30 days[3]. Although the overall size of the population of adolescents who smoke is estimated at approximately 4.3 million high school students and 985K middle-school students, it is possible that the size of the population of smokers in the pediatric population who are seeking to quit smoking and are willing to participate in a clinical trial may, in fact, be too small for studies to be practically conducted. Most 11th and 12th graders, as well as many 10th graders, would likely exceed the age range considered pediatric. Additionally, only a subset of the population considered to be "smokers"" are regular smokers; it is likely that not all are nicotine-dependent and would benefit from nicotine replacement. The Monitoring the Future Study estimated that 2.4% of 8th graders and 5.5% of 10th graders smoke daily, representing less than half of those who have smoked at all in the prior 30 days. Moreover, only smokers interested in quitting and unable to quit on their own would be likely to participate in clinical trials..

It should also be noted that the Surgeon General's Report provides little information on the prevalence of smoking in children under age 12, because current surveys do not collect this information. The National Survey on Drug Use and Health (NSDUH) (unpublished data cited in Surgeon General's Report) noted that, among persons who had ever smoked daily, fewer than 2% began smoking at age 11 or younger.

Based on published studies of adolescent smoking as submitted in the application, adequate and well-controlled studies in smokers less than 18 years are highly impractical for the following reasons:

[2] Preventing Tobacco Use Among Youth and Young Adults: A Report of the Surgeon General, 2012, US Department of Health and Human Services.
[3] 2009 Youth Risk Behavior Survey and 2009 National Youth Tobacco Survey, cited in Surgeon General's Report, 2012.

Although surveys suggest that approximately 5 million high school and middle school students are considered "smokers," meaning they report having smoked on 1-2 days in the past month, a considerable fraction of these smokers are over the pediatric age range generally considered under PREA. Moreover, only about half are likely to be regular smokers, and of these, only a subset would be considered appropriate candidates for nicotine replacement therapy. The population available to enroll in a trial of NRT would need to meet the following criteria:

- Patients must have established addiction (Some occasional smokers may not be nicotine-dependent.)
- Patients should have a history of quit attempts (to establish that they are addicted and motivated to quit)
- Patients must be willing to quit and interested in seeking treatment to help them quit.
- Patients must agree to participate in a clinical trial
- Parents must agree and sign an informed consent
- Patients must have ability to carry the product to school and use it as needed This product, a lozenge intended for p.r.n. use, is not suited to use in schools that have restrictions on self-administration of medication.

Therefore, the sponsor should be granted a waiver for the PMR to conduct a study for smoking cessation in children less than 18 years of age.

1.2 Risk Benefit Assessment

The risk benefit profile of Commit lozenges in the adolescent population cannot be determined at this time.

In terms of efficacy, based on the review of the medical literature in the submission it is still not clear if the potential benefits of NRT (specifically the Commit lozenge) have been adequately evaluated in adolescent patients

In terms of safety, the adverse effects associated with NRT in the adult population can be found in individual product labels and published literature and postmarketing reports. Adverse effects associated with the use of NRT in the adolescent population are available from the published literature as well. In addition, safety data from a PK study conducted by the sponsor involving the nicotine lozenge, nicotine gum and nicotine patch suggests that NRT is generally well tolerated in this population. Final conclusions and recommendations regarding the safety of Commit lozenge in the adolescent population will be detailed the DNCE review.

Based on the review of the sponsor's and the medical literature in the submission the divisions' conclusions are:

- PK parameters from single-dose lozenge exposure appear to be comparable in 13 to 17 year-old adolescents and in adults.
- There is inadequate evidence to support the sponsor's claim of the lack of demonstrated efficacy of nicotine lozenges or any other NRT in adolescents.
- Based on the published studies in adolescents, divisions believe that well controlled efficacy studies in smokers below 18 years of age are impractical and impossible for the reasons noted above

We recommend waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This section is not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no additional recommendations for postmarket requirements or commitments at this time.

2 Introduction and Regulatory Background

2.1 Product Information

Nicotine replacement therapy is the most common form of smoking cessation therapy and has been proven to be effective for the treatment of tobacco dependence in adult patients.

Nicotine polacrilex lozenge is a buccally delivered nicotine replacement product. The lozenge has the same drug substance used in the OTC formulations of Nicorette (nicotine) 2 and 4 mg gum.

Tables of Currently Available Treatments for Proposed Indications

Table 1 summarizes currently available drugs used as aids to smoking cessation.

Table 1: Drugs Used as Aids to Smoking Cessation

Generic/Chemical Name	Trade Name	Dosage Form(s)	Marketing Status	Sponsor(s)
Nicotine polacrilex	Commit Lozenge	Lozenges – buccal delivery system	Prescription (also generic) and Over-The Counter (OTC)	Glaxo SmithKline Consumer Healthcare LP
Nicotine polacrilex	Nicorette gum, chewing	Oral gum pieces	Prescription (also generic) and OTC	Glaxo SmithKline Consumer Healthcare LP
Nicotine inhaler	Nicotrol	Transmucosal Inhaler; oral	Prescription	Pfizer/Pharmacia and Upjohn
Nicotine nasal spray	Nicotrol	Solution with metered spray pump	Prescription	Pfizer/Pharmacia and Upjohn
Nicotine patch	Habitrol	Transdermal film, extended-release	Prescription (also generic)	Novartis
Nicotine patch	Nicoderm CQ	Transdermal film, extended-release	Prescription (also generic)	Sanofi Aventis
Chantix	Varenicline tartrate	Oral tablet	Prescription	Pfizer
Zyban	Buproprion	Oral tablet	Prescription	Glaxo SmithKline

Source: Drugs at FDA

I will note that the safety and effectiveness of nicotine drug products (as noted in Table 1) in pediatric patients has not been established.

2.3 Availability of Proposed Active Ingredient in the United States

There are multiple products that contain the active ingredient nicotine (either OTC or prescription) in the United States including the patch, gum, lozenge, nasal spray and inhaler.

2.4 Important Safety Issues With Consideration to Related Drugs

The use of NRT is associated with a variety of adverse reactions. Pooled randomized controlled therapy using varying NRT formulations found an increased risk of heart palpitations and chest pains, nausea, vomiting, gastrointestinal complaints and insomnia. Pooled evidence specific to the NRT patch found an increase in skin irritations. Orally administered NRT was associated with mouth and throat soreness, mouth ulcers, hiccups and coughing. [4]

[4] Mills EJ, Wu P, Lockhart I, Wilson K, Ebbert JO. Adverse events associated with nicotine replacement therapy (NRT) for smoking cessation. A systematic review and meta-analysis of one hundred and twenty studies involving 177, 390 individuals. *Tobacco Induced Diseases* 2010, 8: 1-15.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The new drug application (NDA #21330), OTC Commit (nicotine polacrilex) 2 and 4 mg lozenges was approved on October 21, 2002 for the reduction of withdrawal symptoms including nicotine craving associated with quitting smoking in adults 18 years of age and older.

2.6 Other Relevant Background Information

At the time of the NDA submission, the application was subject to the FDA's Pediatric Rule [21 CFR 314.55 and 21 CFR 601.27] that being all applications for new active ingredients, new dosage forms, new indication, new routes of administration and new dosing regiments must contain an pediatric assessment of the safety and effectiveness of the product unless this requirement is waived or deferred. The sponsor was granted a deferral of pediatric studies for patients 10-17 years of age until October 31, 2007 and a waiver for pediatric studies for patients under age 10.

In a letter to sponsor (dated 8/19/08) the Division of Nonprescription Products Clinical Evaluation (DNCE) discussed the requirements associated with the Pediatric Research Equity Act of 2003 (PREA) and lozenges for NRT. At a follow-up meeting on February 4, 2009, agreements and action items discussed at the meeting were that the sponsor would:

- Submit an analysis of the existing published literature to demonstrate lack of efficacy of NRT in adolescents and
- Provide PK data to establish the efficacy bridge from nicotine patch and gum formulations to nicotine polacrilex lozenge

In this submission, GSK postulates that the lack of efficacy of nicotine replacement products in adolescents has been established and that no further studies of the product marketed under this application, nicotine polacrilex lozenge are warranted.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

All data and documents in this application were electronically submitted.

3.2 Compliance with Good Clinical Practices

Because the submission consisted of studies from published literature, I cannot determine whether these studies were conducted under Good Clinical Practices Guidelines.

3.3 Financial Disclosures

This section is not applicable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

No new data was submitted to or reviewed by the other review disciplines with the exception of Clinical Pharmacology.

4.1 Chemistry Manufacturing and Controls

This section is not applicable.

4.2 Clinical Microbiology

This section is non-applicable.

4.3 Preclinical Pharmacology/Toxicology

This section is non-applicable.

4.4 Clinical Pharmacology

The sponsor submitted a single-dose pharmacokinetic study (GSK Study S1330074) evaluating the safety, tolerability and pharmacokinetics of NRT (i.e. nicotine patch, nicotine gum and nicotine lozenge) in adolescents. Please refer to Dr. David Lee's review dated 3/26/12 for specific details regarding the clinical pharmacology review of this study. Sections 4.4.1 to 4.4.3 have been deleted.

5 Sources of Clinical Data

As previously mentioned, the sponsor has submitted 12 fully-published articles from the medical literature including: seven randomized, double-blind, placebo-controlled studies, one active-controlled study, two randomized-open-label, controlled studies and two uncontrolled studies.

5.1 Tables of Studies/Clinical Trials

The 12 publications included in the submission are listed in Table 2:

Table 2: Randomized Studies of Nicotine Replacement Therapy (NRT) in Adolescents

Study	N	Age Range	Duration of Treatment	Study Population	Treatments	Other Intervention	Detailed Review Yes or No	If no detailed review, then why not
Randomized, double-blind, placebo-controlled trials								
Roddy et al (2006)	98	12-20	6 weeks Follow-up at 13 weeks	Social and economically deprived adolescent smokers in UK	Nicotine patch Placebo	Behavioral counseling (individual or small group)	Yes	Not applicable
Moolchan et al (2005)	120	13-17	12 weeks	Adolescent tobacco addiction	Nicotine patch Nicotine gum Placebo	CBT (group)	Yes	Not applicable
Wold et al (2005)	50	13-18	10 weeks	Adolescent smokers	Nicotine patch Placebo	Not reported	Yes	Not applicable
Hanson et al (2003)	100	13-19	10 weeks	Adolescent smokers	Nicotine patch Placebo	CBT (individual) Contingency management	Yes	Not applicable
Stotts et al	303	14-19	6 weeks	Male adolescents with spit tobacco addiction	Nicotine patch Placebo UC	Behavioral class (group) UC= 5-10 min counseling with F/U phone call 2 weeks later	Yes	Not applicable
Killen et al (2001)	105	13-18	2 study sessions Session	Adolescent smokers	Nicotine patch Placebo	N/A	No	Inadequate endpoints
Franken et al (2006) Analysis of data from Moolchan et al (2005)	66	13-17	12 weeks	Adolescent tobacco addiction	Nicotine patch + placebo gum Nicotine gum + placebo gum Placebo patch + placebo gum	CBT (group)	No	Inadequate endpoints
Randomized, double-blind, active-controlled trials								

Killen et al (2004)	211	15-18	10 weeks	Adolescent smokers	Nicotine patch + placebo Nicotine patch + buproprion	Skills training	No	Inadequate design (both arms treated with NRT)
Randomized, open-label trials								
Rubenstein et al (2008)	40	15-18	6 weeks	Adolescent light smokers	Nicotine nasal spray + counseling Vs. Counseling	Counseling (group)	No	Inadequate design (open-label)
Hanson et al (2008)	103	13-19	4 week smoking reduction & 4 week treatment	Adolescent smokers	Nicotine patch Nicotine gum Placebo	CBT	No	Inadequate design (open-label)
Uncontrolled trials								
Hurt el al (2000)	101	13-17	6 weeks	Adolescent smokers	Nicotine patch	Strong, personalized messaged based on NCI guidelines as start of treatment Brief behavioral therapy (at subject request)	No	Inadequate design (uncontrolled)
Smith et al (1996)	22	13-17	8 weeks	Adolescent heavy smokers	Nicotine patch	Counseling (group)	No	Inadequate design (uncontrolled)

Source: Sponsor PREA Submission, table 8, Pg. 16-20
Key: CBT =Cognitive Behavioral Therapy

5.2 Review Strategy

GlaxoSmithKline (GSK) submitted 12 published references, seven of which were randomized, double-blind, placebo-controlled studies and the remaining five were either active-controlled, open-label or uncontrolled studies. Of the seven adequate and well-controlled studies, only five included a primary efficacy analyses that assessed quit rates. Therefore, the strategy employed in reviewing the supplement application involved:

- Detailed discussion of the five randomized, double-blind, placebo-controlled studies that assessed efficacy of NRT and;

- Summarized discussion of two randomized, double-placebo, controlled studies (one study assessing withdrawal effects and one study evaluating topography variables as predictors of smoking cessation) are located in the appendix

5.3 Discussion of Individual Studies/Clinical Trials

For the purposes of assessing the efficacy of NRT for smoking cessation in adolescents; five published articles that summarize five randomized, double-blind, placebo-controlled studies will be discussed in detail. The discussion of these studies follows:

Appears this way on original.

Article Title
Use of Nicotine Replacement Therapy in Socieoeconomically Deprived Young Smokers: A Community-Based Pilot Randomized Controlled Trial (Roddy et al) [5]

Study Objective
To determine whether nicotine replacement therapy (NRT), specifically transdermal nicotine when combined with counseling, is effective in young smokers in a deprived area of Nottingham, United Kingdom

Study Design
- Randomized, double-blind, placebo-controlled study
- Population: socioeconomically disadvantaged young smokers (ages 12-20 inclusive)
- Sample size: N=98
- Duration: 6 weeks

Drug Treatments: 1. Nicotine patch (15 mg/10 mg/5 mg) for 2 weeks each
2. Placebo patch
NRT was custom made (Stowic Resources Ltd, Oxford, UK) to ensure identical active and placebo patches.

Inclusion/Exclusion Criteria
To be eligible subjects had to meet the following criteria
- 14-20 years of age and able to give consent
- 12-14 years of age and parental consent obtained,
- Regular smoker (>1 cigarette per day (cpd) or < 1 cpd but past or anticipated withdrawal; carbon monoxide validation >5 ppm
- Have no medical contraindications.

Subjects were excluded if they met any of the following criteria:
- <12 or >20 years of age,
- 12-14 years of age or 14 years of age or over but not competent to consent and parents unable or unwilling to give consent;
- Self-report of non-smoking,
- Allergic to sticking plaster
- Pregnant or risk of pregnancy.

Study Procedures
1. After screening, eligible patients were randomized to receive either active treatment (nicotine patch) or placebo patch

[5] Roddy E, Romilly N, Challenger A, Lewis S, Britton J. Use of nicotine replacement therapy in socieeconomically deprived young smokers: a community-based pilot randomized controlled trial. *Tobacco Control* 2006;15:373-376

2. The active dose schedule was 15 mg/10 mg /5 mg for 2 weeks each for a maximum of 6 weeks
3. Study participants were seen weekly by the study doctor to assess for adverse events and patch dispensing. In addition, counseling was delivered weekly on a one-to-one basis or in small friendship groups by a project youth worker trained in smoking cessation, or a smoking cessation counselor for the adult cessation service in 10-15 minute sessions.

Outcome Measures
Primary outcome measures were carbon monoxide validated quit rates at 4 and 13 weeks. Secondary outcome measures included adverse events and follow-up rates.

Statistical Analysis Plan
The original power calculation for the study was based on recruitment of 550 of the 1080 presumed young smokers in contact with the young project into the study, providing 90% power to detect an increase from 15% cessations in the placebo group to 22% in the active group.

STUDY RESULTS

Disposition
A total of 145 participants volunteered for screening and 98 were deemed eligible for participation in the study. Only 8.2% (8 /98) of study participants completed the study with 37% (N=3/8 of subjects receiving active treatment as compared to 63% (N=5/8) of subjects receiving placebo treatment completed the study. A small percentage of study participants (2.0%) withdrew from the study secondary to an adverse event; with similar rates in both active and placebo treatment groups (50% respectively)

Table 3 provides a summary of demographic, efficacy and safety results from the study.

Table 3: Results of Randomized Controlled Study of Nicotine versus Placebo patches

	Randomised to active treatment	Randomised to placebo treatment
Total numbers	49	49
Mean age in years	14.9	14.7
Percentage female	64	56
Median exhaled CO (ppm)	12.9	11.8
CO validated point abstinence at 4 weeks	5	4
CO validated point abstinence at 13 weeks	0	0
Completed full six week treatment course	3	5
Withdrew because of adverse event	1	1
Other non-severe adverse events*		
Itching	16	7
Rash	6	3
Pain or paraesthesia at patch site	6	4
Dizziness, nausea or headache	2	3

*Some participants experienced more than one adverse effect.
CO, carbon monoxide.

Source: Article (Roddy et al, 2006), Table 2, pg. 375

Baseline demographics were similar between treatment groups. The mean age of patients receiving nicotine patch therapy was 14.9 years. Adherence to therapy was low, the median duration being one week, and 63 participants did not attend any follow-up. At four weeks, five subjects receiving active NRT and two receiving placebo were abstinent, and at 13 weeks no subjects in either the active or placebo treatment groups were reported to be abstinent.

Safety
Results reported for safety were limited. Generally, adverse events were reported more frequently in the active group as compared to the placebo group but none were reported as serious. The most commonly reported AEs in the nicotine patch group were itching, rash, and pain/paraethesia at the patch site.

SUMMARY
The study cited in the reference article was reportedly the first published adequate and well-controlled study of NRT in adolescents in the UK, and did not demonstrate an effect of transdermal nicotine as an aid to smoking cessation in the adolescent population.

There were several deficiencies. The study was too small to demonstrate an effect of transdermal nicotine on smoking cessation rates mostly because of low recruitment

rates and high dropout rates. In addition, the study provides no information about the potential efficacy of the nicotine lozenge, or any other transmucosal product that is dosed on an ad-lib basis, such as gum or inhalator.

Appears this way on original.

Article Title
Safety and Efficacy of the Nicotine Patch and Gum for the Treatment of Adolescent Tobacco Addiction (Moolchan et al 2005) [6]

Study Objective
To determine the safety and efficacy of the nicotine patch and gum for adolescents who want to quit smoking

Study Design
- Randomized, double-blind, double-dummy, 3-arm trial
- Population: Adolescent smokers (13 to 17 years of age, inclusive)
- Sample size: N=120
- Duration: 12 weeks (double-blind treatment)

Study Treatments: 1. Nicoderm (nicotine patch 21 and 14 mg) and Placebo gum
2. Nicorette [nicotine gum 2 and 4 mg) and Placebo patch
3. Placebo patch and Placebo gum

Inclusion/Exclusion Criteria
To be eligible subjects had to meet the following inclusion criteria:
- Males and females, ages 13-17, inclusive
- Female adolescents of childbearing potential were required to have a negative pregnancy test (before being randomized)
- General good health
- Smoked ≥10 CPD for ≥6 months
- Minimal score of 5 on the Fagerstrom Test of Nicotine Dependence (FTND)
- Motivated to stop smoking

Subjects were excluded if they met any of the following criteria
- Drug or alcohol dependence excluding nicotine
- Current mania, psychosis and acute depression (according to DSM –IV)
- Pregnant
- Currently lactating
- Chronic skin conditions
- Use of other tobacco products
- Current use (within the past 30 days) of medications for smoking cessation (e.g. NRT or buproprion)

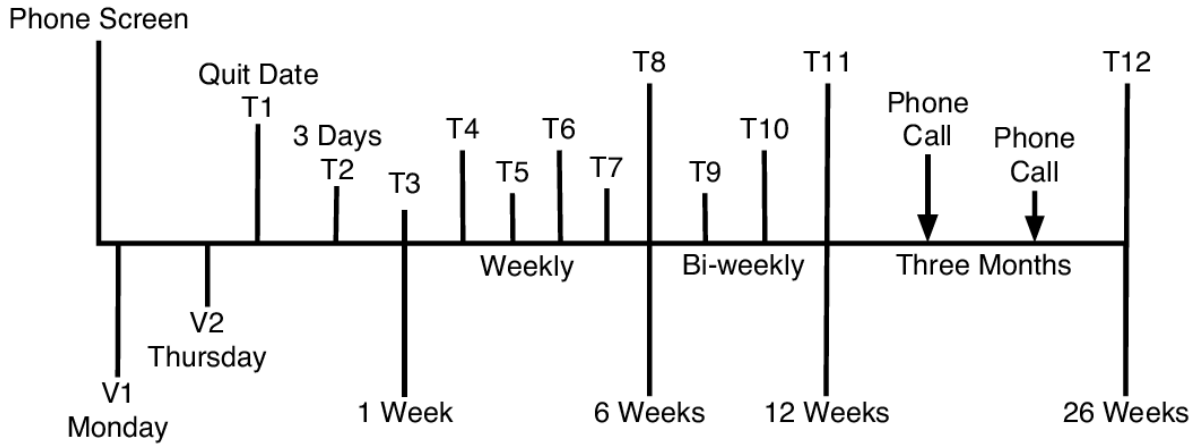
[6] Moolchan ET, Robinson ML, Ernst M, Cadet JL, Pickworth WB, Heishman SJ, Schroeer JR. Safety and Efficacy of the Nicotine Patch and Gum for the Treatment of Adolescent Tobacco Addiction. *Pediatrics* 2005; 115:e407-e114.

Allowed concomitant medications – psychotropic medications not prescribed for smoking cessation

Study Procedures

Figure 1 below illustrates the study timeline

Figure 1: Study Timeline



Source: Article (Moolchan et al, 2005), Figure 1 pg. e409

1. Adolescents who qualified through a telephone screening were invited, along with a parent or guardian to an orientation meeting in which an overview of the study and clinic functions were presented
2. Screening consisted of the following: FagerstromTest of Nicotine Dependence (FTND), sociodemographic assessments, expired-air carbon monoxide (CO) testing, blood, and saliva (for collection of baseline nicotine, cotinine and thiocyanate concentrates) during the 2 baseline clinic visits (V1 and V2)
3. The target quit data was set 1 week after the 2 baseline clinic visits (T1) and on the quit date study participants were instructed in the use of study medications, according to FDA labeling and were given self-help materials from the package insert used for OTC products
4. Eligible patients were randomized to 1 of 3 groups (based on an algorithm by the National Institute of Drug Abuse Pharmacy) with true replacement of trial non-completers. Study participants received one of three treatments for 12 weeks
    a. Nicotine patch and placebo gum
    b. Nicotine gum and placebo patch
    c. Placebo gum and placebo patch
5. Study participants completed a weekly questionnaire documenting the number of cigarettes smoked, tobacco craving and symptoms of withdrawal and depression

Outcome Measures

Efficacy

The trial used the following measures for efficacy

- Prolonged abstinence (defined as continuous abstinence/point prevalence abstinence maintained throughout the study, after an initial 2-week grace period after quit date)) assessed through self-report and verified exhaled CO levels of ≤6ppm
- Point prevalence abstinence (defined as abstinent from smoking if self-report of no smoking during the 7 days before a visit and had an expired CO level of ≤ 6 ppm at that visit)
- Smoking reduction (using CPD and thiocyanate concentrations) among trial completers

Safety

- Adverse events (self-report)
- Saliva cotinine concentrations

Statistical Analysis Plan

Given 3 study groups, for a power of .80 and an *a* level of .05, based on reported values for adult populations 30 and assuming a 70% reduction of smoke exposure in the active-medication groups, the approximate sample size needed to perform an analysis of variance for the main outcome variable (saliva thiocyanate concentrations) was estimated at 17 for each group. [7] Given an anticipated attrition rate of 55%, 40 patients for each group were required to obtain a total of 51 completers.

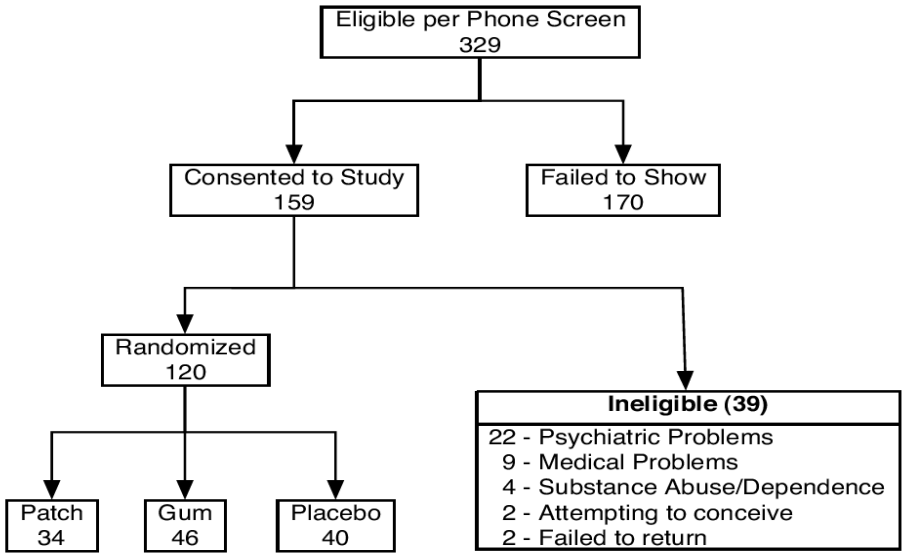
Fisher's exact tests, chi-square tests, and logistic regression analyses were used to assess the effect of treatment group assignment on smoking cessation (both prolonged abstinence and point prevalence abstinence). Treatment groups were coded so that each active treatment arm was compared with placebo.

STUDY RESULTS

Figure 2 illustrates patient enrollment and randomization:

[7] Although this was the protocol-specified primary endpoint, in this review I focused attention on measures of efficacy for smoking cessation, which is the indication at issue in this submission.

Figure 2: Participant enrollment flow chart



Source: Article (Moolchan et al, 2005), Figure 2 pg. e410

Of the 1347 potential study participants who telephoned the clinic, 329 were pre-eligible by telephone screening of which 159 presented for screening and consented to the study. A total of 159 potential study participants were screened; 75% (120/159) met study entry criteria and were randomized and 25% (39/159) were deemed ineligible for the study.

Patient Disposition

Of the 120 participants randomized to receive treatment 44% (53/120) completed the study. The proportion of randomized participants who completed the study were 52.9% (18/34) for the nicotine patch group, 41.3 % (19/46) for the nicotine gum group, and 40% (16/40) for the placebo patch group.

Demographics

A summary of demographics by treatment group is provided in Table 4

Table 4: Participant Demographics

	Patch (n = 34)	Gum (n = 46)	Placebo (n = 40)
Age, y	15.4 ± 1.41	15.0 ± 1.31	15.2 ± 1.29
Female, %	61.8	69.6	77.5
White, %	79.4	65.2	75.0
FTND score	7.00 ± 1.11	7.09 ± 1.39	7.00 ± 1.32
CPD	17.7 ± 6.45	18.9 ± 8.96	19.6 ± 9.70
Age started smoking, y*	12.1 ± 1.87	11.0 ± 1.99	10.9 ± 1.91
Years smoked daily	2.57 ± 1.29	2.73 ± 1.88	2.66 ± 1.35

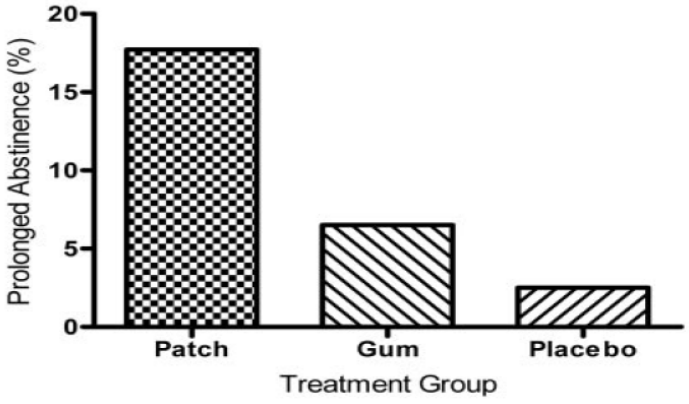
Source: Article (Moolchan et al, 2005), Table 1 pg. e410

Generally, the majority of the study population was female, of Caucasian race, had a mean age of ≥ 15.0 years, smoked an average range of 18 to 20 CPD, had a mean FTND score ≥ 7.0 (indicating high dependence), had an average starting age of smoking of ≥ 11 years and average years of daily smoking of ≥2.6. . e demographic characteristics of patients in the randomized population were similar across treatment groups.

Efficacy

The proportion of study participants who achieved prolonged abstinence is displayed by treatment group in Figure 3 below:

Figure 3: Prolonged abstinence at 3 months (ITT analysis)



Source: Article (Moolchan et al, 2005), Figure 3 pg. e411

The proportion of each treatment group that achieved abstinence follows: nicotine patch group (17.7%, n=6/34); nicotine gum group (6.5% n=3/5); and the placebo group (2.5%, n=1/40) with differences between the nicotine patch and placebo demonstrating statistical significance (p=.043).

Safety

Safety was assessed on the basis of self-reported AEs throughout the study and nicotine and saliva concentrations in saliva. Table 5 summarizes the frequency of AEs by treatment arm. Note that the data are presented on person-time rather than the number of patients per group, which hinders comparison to established rates of adverse reactions associated with these products in the adult population. Additionally, because of the double-dummy design, participants used both patch and gum, either active or placebo, and comparison of route-specific complaints such as "pruritis" and "jaw pain" are difficult to interpret.

Table 5: Adverse Events (Randomized Study Participants) in Order of Decreasing Overall Frequency by Troup Group

	Patch (476 person-wk)	Gum (552.1 person-wk)	Placebo (439.9 person-wk)	Elevated in Active-Medication Group, Compared with Placebo
Pruritus	44	61	25	Patch, $P = .033$; gum, $P = .003$
Erythema	49	39	23	Patch, $P = .0045$
Headache	24	26	36	
Fatigue	15	20	32	
Viral infection	14	30	19	
Insomnia	13	17	13	
Cough	9	15	8	
Nausea	10	10	11	
Jaw pain	10	12	8	
Anxiety	6	13	7	
Sore throat	3	18	3	Gum, $P = .0007$
Hiccups	4	14	4	Gum, $P = .014$
Dyspepsia	4	10	8	
Shoulder or arm pain	15	0	3	Patch, $P = .00011$
Dizziness	3	3	9	
Congestion	3	3	4	
Edema	4	2	4	
Constipation	3	0	0	
Diarrhea	0	0	2	

Source: Article (Moolchan et al, 2005), Table 2 pg. e411

Of the 745 total AEs reported during the study, the most commonly reported AEs were pruritus (130 cases); erythema (111 cases); headache (86 cases); fatigue (67 cases) and viral infection (63 cases). The nicotine patch group had a higher number of AEs reported for erythema, shoulder or arm pain, and constipation as compared to both nicotine gum and placebo treatment groups respectively.

SUMMARY

The results of this study showed that nicotine patch was significantly more effective than placebo in assisting dependent adolescent smokers receiving cognitive behavioral therapy to quit smoking (defined by prolonged abstinence). Also, there was no significant difference between the nicotine patch and nicotine gum on smoking abstinence, and no significant difference between nicotine gum and placebo on smoking abstinence.

The nicotine patch and gum were well tolerated in this study and there was no unexpected safety findings associated with the use of NRT.

Limitations in the study include: low enrollment numbers resulting in relatively small sample size; and a low completion rate. Also, according to the authors of the study, while the large effect size (OR: 8.36) for the comparison of the patch versus placebo for prolonged abstinence suggests a clinically significant effect; the wide CI (95% CI: 0.95–73.3) indicates a lack of statistical power. This may because the study was designed to have sufficient statistical power to detect a significant reduction but not a cessation effect.

Appears this way on original.

Article Title
Nicotine Patch Therapy for Adolescent Smokers: A Pilot Study (Wold et al, 2005) [8]

Study Objective
To assess the safety, feasibility and efficacy of nicotine patch versus placebo patch therapy in adolescents with nicotine and other substance dependence

Study Design
- Randomized, double-blind, placebo-controlled pilot study
- Population: adolescents ages 13-19 in a standard day treatment program for serious conduct and/or substance use problems
- Sample size: N=50
- Duration: 10 week (double-blind treatment)

Study Treatments: 1. Nicotine patch
2. Placebo patch

Inclusion/Exclusion Criteria
To be eligible subjects had to meet the following inclusion criteria
- Smoked >10 CPD
- Had a CO level ≥ 10 parts per million (PPM)
- Not taking buproprion
- Deemed healthy to participate in a clinical trial by the medical director

Study Procedures
1. Eligible patients were stratified by gender and randomized in a 1:1 ratio to either nicotine patch or placebo patch
2. 10 weeks of randomized drug treatment
3. One-month follow-up interview

Outcome Measures (per submission)
- Physical exam, pregnancy test, and blood test (to rule out major disorders and other contraindications)
- Diagnostic Interview Schedule for Children [DISC-IV] (to assess for conduct disorder, major depressive disorder and/or attention deficit hyperactivity disorder)
- Composite International Interview – Substance Abuse Module (to assess the number of abuse/dependence symptoms and give diagnoses of alcohol and ten drug categories)
- Baseline Symptoms Questionnaire

[8] Wold AL, Whitmore EJ, Gianani SK, Mikulich-Gilbertson SK, Nicotine Patch Therapy or Adolescent Smokers: A Pilot Study. *Presented at the College on Problems of Drug Dependence* 2005.

- Smoking history questionnaire
- Daily diaries of adverse events, smoking records and withdrawal symptoms
- Fagerstrom nicotine tolerance questionnaire (score of ≥ 7 suggests a high degree of nicotine dependence)
- Daily Carbon Monoxide (CO) readings

Statistical Analysis Plan
Separate logistic regression analyses were performed on the impact of intake and demographic variables including gender, socioeconomic status, psychiatry morbidity and severity of drug use

STUDY RESULTS

Patient Disposition
Sixty-eight (68%) percent (34/50) of study participants completed the 10-week randomized treatment and 78% (39/50) of participants completed the one month follow-up assessment.

A summary of demographics and descriptive variables for treatment groups is shown in Table 6

Table 6 : Demographics and Descriptive Variables of Study Treatment Groups

Demographics			
		Treatment Groups	
		Nicotine patch	**Placebo patch**
Age (mean ± SD)		16.2 ± .8	16.0 ± .8
Gender (% female)		32	24
Ethnicity % Caucasian % Hispanic % African-American		 68 20 12	 84 16 0
Socioeconomic status [SES] (mean ± SD)		42.9 ± 17.5	43.1 ± 13.7
Descriptive Variables			
		Treatment Groups	
		Nicotine patch	**Placebo patch**
Age of Smoking Initiation	(mean SD)	11.2 2.5	12.1 2.1
Age Began Regular Smoking	(mean SD)	12.2 2.2	12.9 1.4
CO Level (PPM)	(mean SD)	15.7 4.2	13.6 4.9
Number of Cigarettes Smoked Daily	(mean SD)	17.4 6.1	16.1 6.5
Number of Previous Quit Attempts	(mean SD)	1.6 1.7	1.8 1.7
Life Conduct Disorder (%)		76	64
Nicotine Dependence (%)		88	88
Number of Nicotine Dependence Symptoms (mean SD)		4.8 1.8	4.5 1.6
Fagerstrom	(mean SD)	7.6 1.3	7.3 1.2

Source: Wold et al study poster

Demographics between treatment groups were similar. The mean age of study participants in both treatment groups was approximately 16 years of age. Participants randomized to the nicotine patch treatment reported the following: a younger mean age at smoking initiation, younger mean age when regular smoking began, higher mean CO levels, higher mean number of cigarettes per day, a higher mean number of nicotine dependence symptoms and a higher mean Fagerstrom score.

Efficacy

Abstinence

While not listed as an outcome measure, the study poster defined abstinence as no reported smoking for 7 consecutive days and CO levels of 8 ppm or less on those days. A total of 8% (4% in each treatment group) reported smoking abstinence during the study.

Smoking Reduction

Overall, 72% of participants in the nicotine patch group compared to 48% of the placebo patch group reported >80% reduction of daily cigarette use during their time on treatment.

For those participants who completed the 10-week study, those in the nicotine patch group reported reduction of their smoking significantly more than those in the placebo group (reduction of 15 CPD versus 8 CPD respectively, p=0.02)

Safety

No serious adverse events were reported during the study and no participant was prematurely discontinued study because of a safety related event. One participant was withdrawn by the investigator because the participant began taking buproprion while enrolled in the study. Five study participants receiving nicotine patch therapy were referred to the medical director for evaluation of AEs (2 nausea/vomiting events secondary to suspected nicotine toxicity due to continued smoking while wearing the nicotine patch; 1 with exercise-related chest pains, 1 dizziness and the remaining study participant's AE was not identified. The most commonly reported AEs in the nicotine patch group at rates > placebo were redness/itchiness/burning (80%), headache (48%) arm pain (40%) and muscle pain (36%).

SUMMARY

The results of this pilot study shows that while the overall compliance rate for the study was adequate (68%), only 8 % (N-4) of study participants achieved abstinence during the study treatment period. While use of the nicotine patch therapy was generally safe, there were a few AEs related to nicotine toxicity.

Limitations of this study include: the enrolled population did not include many patients that would be considered “pediatric” under PREA and the study provides no information about the potential efficacy of the nicotine lozenge, or any other transmucosal product that is dosed on an ad-lib basis, such as gum or inhalator.

Appears this way on original.

Article Title
Treatment of adolescent smokers with the nicotine patch (Hanson et al, 2003) [9]

Study Objectives
1. Examine the effects of nicotine patch on signs and symptoms of withdrawal form cigarettes among adolescents, adolescent's compliance with the nicotine patch and the safety of the nicotine patch
2. Evaluate the short-term effectiveness of the nicotine patch in helping adolescent to quit smoking

Study Design
- Randomized, double-blind, placebo-controlled pilot study
- Population: adolescents ages 13-19 in a standard day treatment program for serious conduct and/or substance use problems
- Sample size: N=100
- Duration: 13 weeks (10 weeks double-blind treatment)

Study Treatments: 1. Nicotine patch
2. Placebo patch

In conjunction with intensive cognitive-behavioral therapy and a contingency-management program

Inclusion/Exclusion Criteria
To be eligible subjects had to meet the following inclusion criteria
- Smoked at least 10 cpd for at least 6 months
- Did not use any other tobacco products more than 1x/week
- Motivated to quit smoking (e.g. score ≥7 on when asked to rate motivation to quit smoking using scale from 0 [none] to 10[very much]
- Were not currently using nicotine therapy

Subjects were excluded for the following reasons:
- Medically contraindicated
- Current alcohol abuse or drug abuse
- Severe emotional problems in the past year
- Taking psychoactive medications (except those to treat ADHD) in the past 6 months

[9] Hanson K, Allen S, Jensen S, Hatsukami. Treatment of Adolescent Smokers with the Nicotine Patch. *Society for Research on Nicotine and Tobacco* 2003, 5: 515-526.

Study Procedures

Table 7 shows the schedule of study procedures:

Table 7: Schedule of Study Visits

Week	0	1	2	3	4	5	6	7	8	9	10	11	12
Visit	–1 Screening	0 Prequit	1	2	3	4	5	6	7	8	9		10
	Baseline		Cessation treatment										
Physical exam	x												x
Lab tests	x												x
Biochemical													
Salivary cotinine	x	x	x	x	x	x	x	x	x		x		x
CO	x	x	x	x	x	x	x	x	x		x		x
Physiological													
BP/HR	x	x	x	x	x	x	x	x	x		x		x
Weight	x	x	x	x	x	x	x	x	x		x		x
Subjective													
Intake	x												
[1]NWSC	x	x	x	x	x	x	x	x	x		x		x
Adverse events	x	x	x	x	x	x	x	x	x		x		x
Daily diary	x	x	x	x	x	x	x	x	x	x	x	x	x
[2]FTND	x												
[3]ITQ													x

[1]Nicotine Withdrawed Symptoms Checklist.
[2]Fagerström Test for Nicotine Dependence.
[3]Impressions of Treatment Questionnaire.

Source: Hanson et al 2003, pg. 517

Outcome Measures

Fagerstrom Test for Nicotine Dependence
Nicotine Withdrawal Symptom Checklist – e.g. craving, irritability, anxiety, difficulty concentrating, restlessness, impatience, insomnia, increased appetite, drowsiness and depressed mood
Impressions of Treatment Questionnaire
Expired-air carbon monoxide levels
Salivary cotinine samples
Medical history
Heart rate, Blood pressure and body weight
Adverse events

Endpoints

Primary - Nicotine withdrawal (craving and total withdrawal) during first 2 weeks of abstinence
Secondary - Abstinence from cigarettes (at 7-day and 30-day point prevalence)

Point Prevalence abstinence defined as follows:

a. attained CO levels ≤5 ppm at clinic visits within past 7 days (for 7 day point prevalence analysis) or 30 days (for 30-day point prevalence analysis) and

b. report of no cigarettes smoked on the daily diary

Statistical Analysis Plan
Primary outcome measure was examined using a linear mixed model with fixed effects for treatment, time and their intervention. A Bonferroni adjusted significance level of .005 or less was considered to represent a significant difference between treatment groups.

Salivary cotinine levels were analyzed at separate timepoints using Wilcox's nonparametric test of differences between groups.

STUDY RESULTS

Disposition
Of the 375 adolescents who telephoned the clinic to be screened, 59.5% (223/375) met study eligibility criteria. Reportedly, many eligible participants (n=107) never attended the orientation session and medical screening visit. Other eligible participants attended the orientation session and medical screening but never returned (n=16). Reasons participants were considered ineligible included; 15.2% (n=57) consumed greater than 3 alcoholic beverages per occasion and 9.8% (n=37) were currently experiencing depression.

A total of 100 adolescents started the study with 53% (n=53) reported to have completed treatment. Follow-up rates among the 53 treatment completers were 49% at 14 weeks and 38% at 36 weeks.

Demographics
Table 8 summarizes the demographics of study participants

Table 8: Demographics of study participants (N=100)

Measure	Overall mean ± *SD*	Active mean	Placebo mean	*p* value
Cigarettes (per day)	16.3 ± 4.9	16.6	16.0	0.56
Age (years)	16.8 ± 1.5	17.0	16.6	0.24
CO (ppm)	14.2 ± 7.0	14.9	13.4	0.30
Weight (lb)	149.4 ± 35.6	150.8	148.0	0.70
SBP (mmHg)	113.6 ± 10.3	115.6	111.7	0.06
Age first cigarette(years)	11.8 ± 2.6	11.9	11.8	0.85
Age daily smoker (years)	13.5 ± 2.0	13.4	13.6	0.79
Alcoholic drinks/occasion[a]	03.7 ± 3.3	03.8	03.7	0.91
Number of quit attempts	04.1 ± 6.4	05.1	03.1	0.11

Source: Hanson et al 2003, Table 2, pg. 520

Overall, study participants had a mean age of 16.8 years with a standard deviation of 1. 5 years. The mean number of CPD of 16.3, mean age of first cigarette use of 11.8 years, and mean number of quit attempts of 4. The demographic characteristics of study participants were similar across treatment groups.

Efficacy results

Withdrawal symptoms

Reported results showed the nicotine patch group had a statistically significant lower craving score compared to the placebo patch group (p=0.011) and a lower overall mean withdrawal symptom score (p=.025) at 2 weeks post-quit.

Point prevalence abstinence rates (30-day)

Thirty –day point prevalence abstinence rates are shown in Table 9.

Table 9: Thirty-day Point Prevalence Among All Subjects (n=100)

	active group		Placebo group		
Time postquit	% Abstinent	*SD*	% Abstinent	*SD*	*p* value
4 weeks	22.0	.41	12.0	.32	0.29
5 weeks	22.0	.41	14.0	.35	0.43
6 weeks	24.0	.43	18.0	.38	0.62
8 weeks	18.0	.38	18.0	.38	1.00
10 weeks	20.0	.40	18.0	.38	1.00

Abstinence rates reported are for the 30 days preceding the time post-quit. Dropouts were considered to have relapsed to smoking.

Source: Hanson et al 2003, Table 4, pg. 522

The 30-day point prevalence analyses showed no significant differences between nicotine patch and placebo patch on abstinence rates. For example, for the 5 weeks time, the results of the analyses shows that in the preceding 30 days there was no statistically significant difference

Safety results

No serious adverse events were reported during the study and no participant was prematurely discontinued as a result of an AE. The majority of AEs were reported as mild in severity.

Of study participants, 97.9% of the nicotine patch group as compared to 93.7% of the placebo patch group experienced an adverse event. The most common adverse events reported by participants in the nicotine patch were itching at the site (64.5%), sleep problems or abnormal dreams (62.5%), joint or muscle aches (58.3%), redness at

nicotine patch site (54.2%,), lightheadness/dizziness (41.7%) and stomachaches (43.8%).

SUMMARY

The primary objective of the study cited in the article was to examine the effects of the nicotine patch on craving, withdrawal symptoms, safety and compliance; and the secondary objective was to evaluate the effectiveness of the nicotine patch in helping adolescents quit smoking. Results of the study show no difference between nicotine patch and placebo in helping adolescents to quit smoking.

Limitations of the study include: low enrollment rate, low completion rate [nearly half of participants dropped out (for reasons unknown) and low follow-up rates. In addition, study participants had an average age of 16.8 years; which is at the upper age range (17 years) the sponsor has been asked to study. The information in this study may not useful to understand tobacco addiction in younger adolescent patients (e.g. 12 -14 year-olds) or in the 10-11 age group also included in the studies required under PREA.

Appears this way on original.

Article Title
A randomized clinical trial of nicotine patches for treatment of spit tobacco addiction among adolescents (Stotts et al, 2003) [10]

Study Objective
Evaluate the efficacy of nicotine patches in combination with behavioral therapy for the treatment of adolescent spit tobacco addiction

Study Design
- Randomized, double-blind, placebo-controlled study
- Population: adolescent males, ages 14-19 with regular use of spit tobacco for previous year
- Sample size: N=303
- Duration: 6 weeks (follow-up through 1 year)

Study Treatments: 1. Nicotine patch
- Light to moderate users (<150 ng/ml in baseline saliva sample) 14 mg x 3 weeks followed by 7 mg x 3 weeks
- Heavy users (≥150 ng/ml in baseline saliva sample) 21 mg X 2 weeks, 14 mg x 2 weeks and 7 mg x 2 weeks
2. Placebo patch
3. Usual Care – 10 minute counseling with follow-up call in 2 weeks

In conjunction with group behavioral intervention classes

Inclusion/Exclusion Criteria
To be eligible subjects had to meet the following inclusion criteria
- Adolescent males with regular use of spit tobacco (ST) currently and for the previous year. Regular use was defined as using either snuff or chewing tobacco ≥5 of 7 days per week. If they were concurrent cigarette smokers, they also had to agree to quit smoking at the same time as ST cessation
- Motivated to quit ST

Subjects were excluded if they met the following criteria:
- Female
- Unwilling to quit all forms of tobacco or be randomized

[10] Stott RC, Roberson PK, Hanna EY, Jones SK, Smith CK. A randomized clinical trial of nicotine patches for treatment of spit tobacco addiction among adolescents. *Tobacco Control* 2003;12:iv11-iv15.

Study Procedures

1. After initial recruitment from 41 high schools throughout Arkansas with the aid of radio ads and internet website; study organizers received permission for principals at

these high schools to give a presentation on the dangers of ST use and the research study being conducted
2. All students were invited for a free oral screening and ST users were invited to participate in the study with subjects ages 14-17 years of age needing parental consent and assent for themselves Students 18-19 years of age were given consent forms that did not require parental signatures
3. Eligible students were randomized into one of three treatment groups: usual care, nicotine patch and placebo patch.
    a. Usual care study subjects received a 5-10 minute counseling followed by a phone call two weeks later to assess tobacco use status. No further interventions were provided. Phone calls at 6 months post-intervention were used for tracking purposes. At one year, subjects in this group were asked to complete a telephone interview to determine tobacco use status
    b. Subjects randomized to one of the patch groups were asked to provide baseline saliva samples for cotinine testing.
        i. Subjects with continue values <150 ng/ml were considered light to moderate users and followed nicotine patch dosing: 14 mg x 3 weeks, followed by 7 mg X 3 weeks. Subjects with ≥150 ng/ml were considered heavy users and followed nicotine patch dosing: 21 mg x 2 weeks, 14 mg x 2 weeks and 7 mg x 2 weeks. Subjects with no cotinine level were dropped from the study.
        ii. Both nicotine and placebo patch groups received 6 weeks of 50 minutes behavioral intervention classes based on the National Cancer Institute educational materials.
        iii. Between weeks 3-4, subjects in both patch groups selected a quit date, received their randomized patch therapy and continued this treatment for 6 weeks.
            - Subjects were encouraged to report adverse events and other symptoms by calling a toll-free number anytime.

            - Follow-up calls were made to subjects in patch groups at the following post-intervention times: 2 weeks, 4 weeks, 8 weeks, 3 months, 9 months, and 12 months. Each call involved stage based counseling and assessment of tobacco use status.

Outcome Variables

- 30-day point prevalence rates of abstinence for all tobacco groups
- ST use alone at one year follow-up

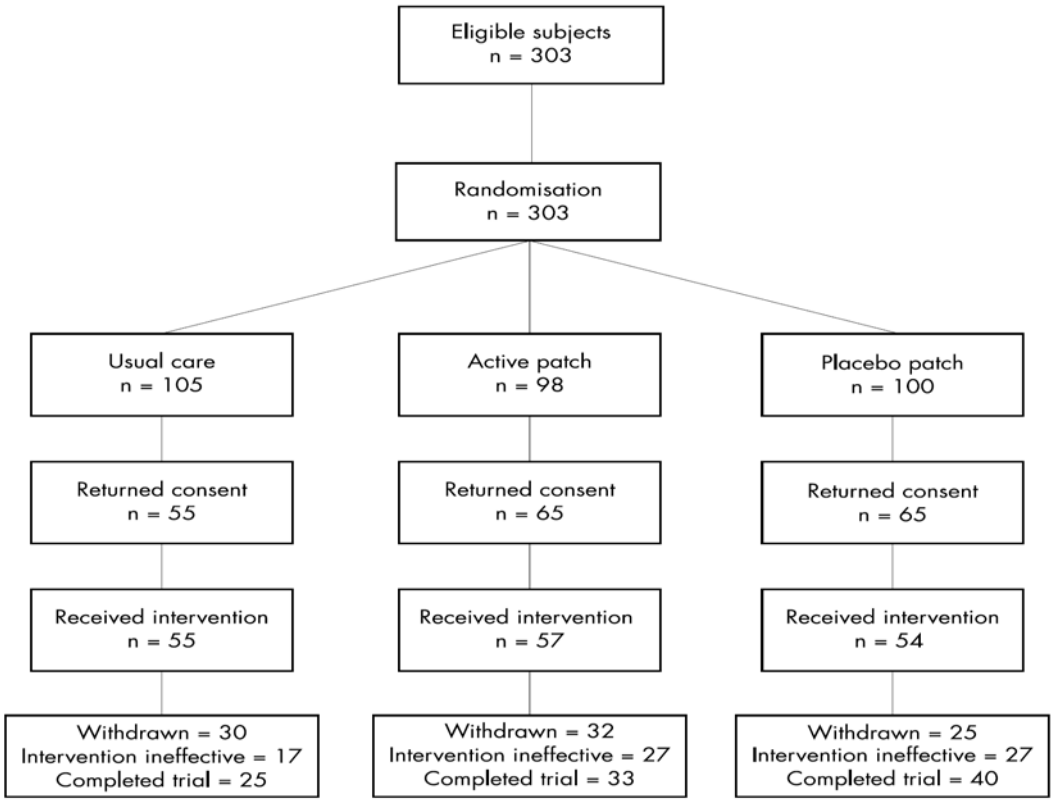
Statistical Analysis Plan
The used an "intention to treat" model, and for all subjects who did not provide information at any time point were considered relapsers for that data collection period. Based on power calculations, each arm needed 75 subjects to have 80% power to

detect differences in quit rates between active and placebo patch groups of 48% and 25% respectively at the 0.05 level. The sample sizes of subjects randomized to each arm were increased to allow for attrition.

STUDY RESULTS

Disposition
Figure 4 that follows displays the disposition of study participants.

Figure 4: Study Disposition



Source: Stotts et al article, Figure 1, pg. 3 of 6

A total of 303 subjects were enrolled and randomized with similar distributions to each treatment groups. Of note, only 52% of the usual care group, 66% of the nicotine patch group and 65% of the placebo group returned their consent forms. A total of 98/303 study participants that were originally enrolled completed the study (25 in the usual care

treatment group, 33 in the nicotine patch treatment group and 40 in the placebo patch treatment group 130 remained in the study for 1 year.

Baseline Characteristics of Study Population
Of note, only subjects who returned consent forms were included in this analysis. The median age of study participants was 17 years, the majority of participants were Caucasian, and 40% of participants were seniors in high school.

Efficacy
Table 10 shows tobacco use abstinence at baseline, six months and one year. According to the authors, the procedure for enrolling subjects had to be modified from the standard for randomized clinical trials.

Table 10: Tobacco Use Abstinence at Baseline, Six months and One Year

	Usual care (n = 105)	Nicotine patch (n = 98)	Placebo patch (n = 100)	Both patch groups (n = 198)
Time 0 (post-classes)				
Spit tobacco* (%)	3.8†	31.6	29.0	30.3
6 months				
Spit tobacco (%)	N/A‡	15.3	17.0	16.2
1 year				
Spit tobacco (%)	11.4	17.3	25.0	21.2
Snuff (%)	12.4	18.4	26.7	22.6
Chew tobacco (%)	22.9	29.6	36.0	32.8
Cigarette (%)	14.3	12.2	23.0	17.7
All tobacco (%)	7.6	6.1	13.0	9.6

*Spit tobacco = snuff and chew tobacco combined—that is, percentage of subjects who used neither form.
†Time 0 for usual care is 2 week follow up; for patch groups, time 0 = end of the 9 weeks of behavioural and patch intervention.
‡Usual care subjects were not queried about tobacco status at 6 months.

Source: Stotts et al article, Table 2, pg. 5 of 6

The usual care group had a low abstinence rate (3.8%) for ST at the end of their intervention (2 weeks.), however the abstinence rate increased to 12.4% at one year even though they did not receive any interventions. There was no significant difference in the ST abstinence rate between the nicotine and placebo patch groups at 9 weeks (31.6% vs. 29% respectively); 6 months (15.3% vs. 17.0% respectively) and 1 year (17.3% vs. 25.0% respectively). With respect to the cigarette abstinence at 1 year, the placebo group had a higher percentage of participants reporting abstinence compared to the nicotine patch group (23.0% vs. 12.2% respectively).

Safety
There were no serious adverse events reported among study participants. Two subjects on patch therapy (not documented as to whether active vs. placebo patch)

were removed from patch therapy within the first week secondary to headaches. Minor AEs including skin irritation (3 subjects) and headaches (2 subjects) were reported however the article does not indicate which treatment groups these AEs occurred in.

SUMMARY
In summary, the results of the study shows that use of the nicotine patch does not provide improvement over placebo patch when attempting to quit ST, snuff, chew tobacco and cigarettes. Further, at one year following treatment it appears that the nicotine patch does not offer improvement over minimal or no contact interventions (e.g. usual care).

Limitations of this study include: low study completion rates; and participants who did not return consent forms were considered failures in all subsequent analyses. Study participants were older adolescents (e.g. seniors in high school with a median age of 17 years). The applicability of efficacy and safety data results to younger adolescent patients (e.g. aged 12-14 yeas old) or preadolescent patients would be limited.

This study provided no information about the potential efficacy of nicotine lozenge, or any other transmucosal product that is dosed on an ad-lib basis, such as gum or inhalator.

6 Review of Efficacy

Efficacy Summary

No adequate and well-controlled studies efficacy and safety studies were conducted by the sponsor in support of this application.

6.1 Indication

Commit (nicotine polacrilex lozenge) 2 and 4 mg is approved as an OTC drug product for the indication " to reduce withdrawal symptoms, including nicotine craving, associated with quitting smoking for adults 18 years and older. "

6.1.1 Methods

Five randomized, placebo-controlled studies discussed the efficacy of NRT therapy (mainly nicotine patch) in adolescent smokers.

6.1.2 Demographics

Generally, demographics of study participants were similar across studies. Of note, variations did occur across studies with respect to severity of tobacco addiction and inclusion of "special" adolescent populations (e.g. homeless). Please refer to Section

5.3 – Discussion of Individual Studies for specific details regarding demographics of study populations.

Several of the studies reported an average age of study participants greater than 16 years; one study enrolled primarily high school seniors.

6.1.3 Subject Disposition

Overall, the majority of studies had low enrollment rates, high dropout rates with subsequent low rates of completion. At least one study failed to enroll the protocol-specified sample size that was calculated as necessary for statistical comparisons. This may be due to slow accrual in single-site studies, and time limits on grant-funded research.

6.1.4 Analysis of Primary Endpoint(s)

The Division of Anesthesia, Analgesia and Addiction Products (DAAAP) generally defines smoking cessation as: 1) a quit rate of ≥4 weeks by self report and 2) confirmed biological evidence of quitting (e.g. exhaled carbon monoxide)

In the studies that evaluated the efficacy of NRT, primary endpoints varied and appear not to be consistent with DAAAP's interpretation of smoking cessation/abstinence. Examples of these primary endpoints include: prolonged abstinence, point prevalence abstinence (i.e. 7 day), smoking reduction, and nicotine withdrawal. Where an endpoint resembling DAAAP's preferred endpoint was reported, emphasis was placed on this analysis in the review.

7 Review of Safety

Safety Summary

The safety profile of NRT (mainly nicotine patch therapy) was assessed in five, adequate and well-controlled studies. Generally, NRT was tolerated by study participants. No unusual or expected events occurred in these studies. Adverse events related to nicotine patch therapy included: itching, redness and burning at the patch

site, headache and arm pain. Of note, there was limited enrollment of patients under the age of 16, making it difficult to draw conclusions about the safety in that population.

Please refer to DNCE's review for a discussion of postmarket safety. .

8 Postmarket Experience

Currently, nicotine polacrilex lozenge is an OTC drug product approved and marketed in the United States as Commit lozenges. As reported on the carton label, the following are known side effects associated with nicotine lozenge use: warm tingling mouth sensation, allergic reactions, irregular heart beat, mouth pain, sore throat, persistent indigestion and tightness in chest.

9 Appendices

9.1 Literature Review/References

See Footnotes throughout review.

9.2 Postmarket Evaluation

Nicotine polacrilex lozenges is approved and marketed in the U.S. as an OTC drug product

9.3 Labeling Recommendations

DAAAP and DNCE collectively propose the following label recommendations for the directions:

"If you are under 18 years of age, ask a doctor before use. (b) (4) (b) (4) **"**

9.4 Advisory Committee Meeting

No advisory committee meeting is associated with this application.

9.5 Additional Studies

Article Title
Smoking Rates and Topography Predict Adolescent Smoking Cessation Following Treatment with Nicotine Replacement Therapy (Franken et al, 2006) [11]

Study Objective
To determine if high baseline smoking rates and topography measures would inversely predict smoking cessation among adolescent smokers

Study Design
Randomized, double-blind, double-dummy, 3-arm trial

- Population: Adolescent smokers (13 to 17 years of age, inclusive)
- Sample size: N=66
- Duration: 12 weeks (double-blind treatment)

Study Treatments: 1. Nicoderm (nicotine patch 21 and 14 mg) and Placebo gum
2. Nicorette [nicotine gum 2 and 4 mg) and Placebo patch
3. Placebo patch and Placebo gum

In conjunction with cognitive behavioral therapy

Inclusion/Exclusion Criteria
To be eligible, subjects had to meet the following inclusion criteria:

- Ages 13 to 17 (inclusive)
- Smoked at least 10 CPD for 1 year
- Fagerstrom test of nicotine dependence score ≥5

Subjects were excluded for the following reasons:

- Pregnancy
- Recent use of NRT
- Untreated acute psychiatric disorder (including current drug or alcohol dependence)
- Lack of parental permission

Study Procedures
1. After 2 baseline visits, eligible participants were enrolled and randomized into one of three treatment groups: active patch/placebo gum, active gum/placebo patch or placebo gum/placebo patch.

[11] Franken FH, Pickworth WB, Epstein DH, Moolchan ET. Smoking Rates and Topograph Predict Adolescent Smoking Cessation Following Treatment with Nicotine Replacement Therapy. *Cancer Epidemiology, Biomarkers & Prevention* 2006;15(1): 154-157.

2. Thereafter, participants returned for their scheduled quit date and on the quit date they were instructed to use the gum as need (with the approximate recommended daily use being equivalent to half of their baseline PD) and to apply a new patch daily
3. Thereafter, participants had 11 treatment visits over 12 weeks. At each treatment visit, participants attended a 45-minute cognitive behavioral group therapy session led by trained social workers.
4. Follow-up consisted of a 3 month post-quit visit

Outcome Measures

- Point prevalence abstinence – at each visit defined as self-reported abstinence from smoking an expired CO level of <6 ppm
- Prolonged abstinence at end of treatment – defined as point prevalent abstinence maintained throughout the 12 weeks of the trial, with the exception of an initial 2-week grace period immediately following the quit date
- Point-prevalent abstinence 3 months after the end of the study

Statistical Analysis Plan (direct from article)

Descriptive statistics were calculated to characterize demographic variables, smoking patterns, and topography measures. Because this was a sample of convenience, the sample size was dictated by the power analysis for the clinical trial. Predictors of abstinence were first examined in bivariate tests (m2 tests for categorical measures and t tests for continuous variables). Topography measures and covariates with P values below an initial threshold of 0.20 were tested in a backward stepwise logistic regression model of continued smoking along with treatment group (patch versus gum) which was selected a priori as a controlling variable. Because no measure of nicotine dependence has shown predictive validity for adolescents receiving nicotine replacement therapy, dependence level was not designated as a controlling variable. Topography variables with $P > 0.2$ associations were dropped from the model. Predictors contributing to the stepwise model were compared using t tests to determine their associations with smoking abstinence at the 3-month follow-up visit. All analyses were done on an intent-to-treat basis. $P < 0.05$ was used as a test of significance.

Authors report due the extremely low rate of abstinence in the third group (placebo gum/placebo patch), the analyses included only data from adolescents in the first two groups (those receiving active NRT)

STUDY RESULTS

Disposition

At the end of the 3 month treatment period, 12% of participants were reported to have achieve prolonged abstinence, at the 3 month follow-up, 15% were point prevalent abstinence.

Predictors of Abstinence

End of treatment

End of treatment (12 weeks) abstinence was predicted by baseline CPD and by puff volume. At the 3-month posttreatment follow-up visit abstinence was reportedly significantly associated with puff volume.

Safety

Not evaluated in this article.

SUMMARY

In summary, this study was not designed to recruit tobacco-addicted adolescent, nor was it designed to evaluate efficacy of NRT. The study attempted to predict the reliability of exposure variables such as CPD and smoking topography measures of adolescent smoking cessation and by proxy degree of tobacco dependence. Study results appear to show that markers of the frequency and intensity of smoke exposure such as CPD and smoking-topography measure may be useful predictors of adolescent smoking cessation, and by proxy, degree of tobacco dependence.

Limitation of the study included the sample size, selection criteria, research setting (e.g. topography machine) and findings not generalizble to youths who are experimenting with smoking and have not graduated to high levels of daily smoke exposure.

Article Title
Do Adolescents Smokers Experience Withdrawal Effects When Deprived of Nicotine (Killen et al, 2001) [12]

Study Objective
1. To study the effects of nicotine deprivation in adolescent smokers over a 8 hour period
2. To evaluate if brief treatment with NRT would alleviate symptoms of nicotine withdrawal

Study Design
- Randomized, double-blind, placebo-controlled study
- Population: adolescent smolders, ages 13-18 from homeless shelter and alternative high schools
- Sample size: N= 105
- Duration: 2 study sessions (Session 1 – 8 hours, Session 2

Study Treatments: 1. Nicotine patch (15 ug)
2. Placebo patch

Inclusion/Exclusion Criteria
To be eligible, subjects had to meet the following inclusion criteria:
- Ages 13 -18 (inclusive)
- Smoke a minimum 10 CPD
- Expired CO level ≥5 ppm

Subjects were excluded for the following reasons:
- Current daily use of illicit drugs or alcohol
- Current diagnosis of major depression
- Current pregnancy
- Current breastfeeding
- No health contraindications to use of nicotine patch

Study Procedures
The study consisted of screening and 2 treatment sessions conducted over 2 consecutive Saturdays

Session 1
1. Patients smoked normally over an 8 hour period

[12] Killen JD, Ammerman S, Rojas N, Varady J, Haydel F, Robinson TN. Do Adolescent Smokers Experience Withdrawal Effects When Deprived of Nicotine? *Experimental and Clinical Psychopharmacology* 2001, Volume 9, No 2: 176-182

2. Subjective withdrawal symptoms (e.g. depressed mood, anxiety, difficulty concentrating, sleepiness, restlessness, frustration, anger and hunger) were assessed at 4-hr intervals and vitals (blood pressure and heart rate) and CO level were assessed at 2-hr intervals over a period of 8 hr.

Session 2

1. Seven days later participants were randomized to wear either 15-mg nicotine patch for 16 h or a placebo patch for 8 hr and were to refrain from smoking during the session
2. Similar to session 1, subjective withdrawal symptoms were assessed at 4-hr intervals and vitals (blood pressure and heart rate) and CO level were assessed at 2-hr intervals over a period of 8 hr.
3. Participants were withdrawn from the study if a CO level increased from any previous level during this session and patients were advised to refrain from secondhand exposure. Exceptions were made for CO levels that remained at or below 5 ppm but increased no more than 3 ppm
4. After completion of this session, participants were asked to guess their patch assignment and whether they experienced any side effects related to the patch
5. Finally, at the end of this session study participants were encourage to maintain abstinence and were provided smoking cessation materials

Outcome Measures

- Nicotine withdrawal symptoms (depressed mood, anxiety, difficulty concentrating, sleepiness, restlessness, frustration, anger, and hunger)
- Vitals (heart rate and blood pressure)
- Expired-air CO levels
- Modified Fagerstrom Tolerance Questionnaire (mFTQ)
- Adverse events

Statistical Analysis Plan

Primary endpoint analysis - Difference in the Session 2 endpoint values with the final vales obtained 1 week earlier at the end of Session 1

Slope analysis – difference in the least squares regression slopes fitted to the data points obtained throughout the day

STUDY RESULTS

Disposition

One hundred five adolescent smokers attended Session 1. A total of 13 participants were excluded from the study (8 – failure to attend Session 2; 2- smoking during Session 2; 2-protocol violations and 1- adverse event of nausea). The sample size used for the analysis was 92.

Table 12 shows the effects of nicotine deprivation:

Table 12: Effects of Nicotine Deprivation

	Placebo			Active patch			
Measure	Session 1	Session 2	p^a	Session 1	Session 2	p^b	p^c
Heart Rate							
Endpoint	86.61	80.41	<.001	86.82	84.42	.18	.09
Slope	0.46	−1.10	<.001	0.14	−0.25	.28	.02
Systolic BP							
Endpoint	117.70	115.78	.27	114.39	118.47	.01	.01
Slope	0.19	0.00	.62	−0.15	0.81	.02	.04
Diastolic BP							
Endpoint	60.54	60.44	.92	60.98	64.28	<.01	.02
Slope	−0.26	−0.33	.71	−0.24	0.47	<.001	<.01
Craving							
Endpoint	4.44	6.37	<.001	4.33	6.20	<.01	.92
Slope	−0.30	0.50	<.001	−0.03	0.39	<.001	.68
Depression							
Endpoint	1.83	2.30	.16	2.29	2.53	.66	.73
Slope	−0.01	0.03	.36	0.07	0.02	.49	.27
Sleepiness							
Endpoint	3.74	2.72	.04	4.00	2.91	.05	.92
Slope	−0.07	−0.19	.20	−0.07	−0.27	.02	.52
Frustration							
Endpoint	2.28	3.28	.03	3.02	3.80	.13	.74
Slope	−0.06	0.13	.01	0.08	0.18	.11	.31
Anger							
Endpoint	1.68	2.26	.12	2.91	3.27	.53	.74
Slope	−0.01	0.05	.31	0.09	0.16	.28	.92
Anxiety							
Endpoint	3.32	5.19	<.001	2.93	5.40	<.001	.43
Slope	−0.09	0.27	<.001	−0.11	0.28	<.001	.81
Concentration							
Endpoint	2.43	3.13	.09	2.73	2.96	.67	.47
Slope	−0.07	0.09	.03	−0.03	0.05	.26	.45
Hunger							
Endpoint	1.79	1.85	.82	2.14	1.75	.28	.32
Slope	−0.44	−0.32	.11	−0.24	−0.28	.55	.12
Restlessness							
Endpoint	2.66	4.17	<.001	2.53	3.80	<.01	.70
Slope	−0.05	0.23	<.001	−0.09	0.19	<.001	.94

[a] Session 1 versus Session 2 for placebo patch. [b] Session 1 versus Session 2 for active nicotine patch. [c] Active nicotine patch versus placebo patch.

Source: Article - Killen et al 1002, Table 2 pg. 179

When comparing Session 1 versus 2 in the nicotine patch group, there were increases in systolic and diastolic BP, increases in craving, increases in anxiety ,and increases restlessness that were statistically significant. When comparing nicotine patch versus placebo patch, no statistically significant differences were noted between these groups

in symptoms of craving, depression, sleepiness, frustration, anger, anxiety, concentration, hunger and restlessness.

Safety
There were no serious adverse events reported during the study. Overall, there were 16 severe AEs reported in the nicotine patch group compared to 4 severe AEs reported in the placebo patch group. The most commonly reported AEs in the nicotine patch group were itching and dizziness.

SUMMARY
In summary, the cited in the article was designed to evaluate efficacy of NRT in adolescent smokers. The study was reportedly the first controlled prospective study of the effects of nicotine deprivation in adolescent smokers. Overall, the study suggests that adolescent smokers exhibit signs and symptoms associated with abrupt withdrawal of nicotine; no meaningful differences were noted between NRT and placebo when treating these nicotine withdrawal symptoms.

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/s/

JACQUELINE A SPAULDING
04/04/2012

CELIA J WINCHELL
04/11/2012

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21-330/S-013
Priority or Standard	Standard
Submit Date(s)	8/9/2011
Received Date(s)	8/9/2011
PDUFA Goal Date	6/9/2012
Division / Office	DNCE/ODE IV
Reviewer Name(s)	Priscilla Callahan Lyon, M.D.
Review Completion Date	4/10/2012
Established Name	Nicotine Polacrilex Lozenge
(Proposed) Trade Name	Nicorette Lozenge
Therapeutic Class	Nicotine Replacement Therapy
Applicant	GlaxoSmithKline
Formulation(s)	Oral Lozenge, 2 mg and 4 mg
Dosing Regimen	If you smoke your first cigarette within 30 minutes of waking up use 4 mg nicotine lozenge according to the 12 week schedule below: If you smoke your first cigarette more than 30 minutes after waking up use the 2 mg nicotine lozenge according to the 12 week schedule below:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

Indication(s)	Smoking Cessation Aid
Intended Population(s)	Children under 18 years of age

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This supplement application from GlaxoSmithKline (GSK) was submitted to comply with requirements specified in the Pediatric Research Equity Act (PREA). Specifically, GSK was required to address the efficacy and safety of the drug product (nicotine polacrilex lozenges, 2 mg and 4 mg) for use in the pediatric population ages 10 to 17 years. Study of safety and efficacy for patients < 10 years of age was waived at the time of NDA approval.

To address safety, GSK included data from their pharmacokinetic study conducted on subjects ages 13 to 17 years, data from several published literature reports of studies conducted on adolescent populations using other NRT products, and a review of the GSK post-marketing data for all reports for patients < 18 years of age involving nicotine drug products for a three year period. No new safety signals were identified.

GlaxoSmithKline does not believe NRT products are efficacious in the adolescent (<18 years of age) population. To support this rationale, this supplemental application includes data from multiple investigators in the published literature. None of these studies provide convincing evidence for efficacy of NRT in the adolescent population; however, there were significant flaws in the studies including difficulty with enrollment (particularly subjects < 13 years of age), very high drop-out rates, and small sample sizes.

GSK proposes changes to the product labeling regarding the lack of efficacy in those < 18 years of age. The sponsor believes the data submitted and the proposed labeling change should release them from obligations for additional pediatric study of this product.

The application should be approved; GSK should be released from additional obligations for pediatric study of this drug product. The data submitted with this supplement application have documented that study of NRT products in subjects < 18 years of age is 'impractical and impossible.' The sponsor has adequately demonstrated through literature reports from multiple investigators that these studies cannot be completed in a way that meets current FDA regulatory requirements; therefore the PREA requirement should be waived and the company should be released from pediatric study obligations for this drug product. The sponsor demonstrated that the nicotine pharmacokinetic parameters for adolescents ages 13-17 years old are comparable to the historical adult nicotine pharmacokinetic parameters. This application will be discussed with the Pediatric Review Committee and appropriate language for the labeling change will be negotiated prior to final action.

1.2 Risk Benefit Assessment

As noted above, review of the safety data did not reveal any new safety concerns. During the pharmacokinetic study, the most commonly reported AEs were nausea, pharyngitis, eructation and anemia; only nausea, pharyngitis and eructation were deemed by the investigator to be treatment-related adverse events. All but one of the reported events were considered by the investigator to be mild or moderate in intensity; the only AE that was classified as severe was "throat burn" (reported by subject number 63 in the Nicorette 4 mg gum group). Two subjects were discontinued due to adverse events. They both reported nausea and vomiting, which were considered to have a highly probable relationship to the study medication. There were subjects who developed anemia during the study; this was believed to be due to the quantity of blood drawn during the study.

The published literature reports also did not indicate any new safety concerns. The NRTs administered in these studies were the nicotine patch (five reports) and nicotine gum (one report). Cutaneous reactions and headaches were the most common complaints, but overall, the general pattern of adverse events was similar to the known results from studies in adults. There was no evidence of any significant safety concerns specifically associated with administration of NRT products to adolescents.

The GSK worldwide clinical safety database was searched on 26 October 2011 using the following criteria:

- **Data lock point(s):** 31 October 2007 to 30 October 2010
- **Report types:** All spontaneous reports, post-marketing surveillance reports, and unblinded serious clinical trial reports (attributable and non-attributable).
- **Suspect drug:** nicotine patch and nicotine polacrilex (gum and lozenge)
- **Age:** less than 18 Years (Exposure to nicotine via breast milk and in-utero exposure reports have been excluded.)

There were 68 reports retrieved. Most of the reports of adverse events in children (< 12 years of age) were due to accidental exposure to single doses of nicotine. In several cases (n=7), there were no associated symptoms related to the nicotine exposure and the majority of the reported events were gastrointestinal complaints (nausea and vomiting) or neurological events (tremor or dizziness). Most of the adverse event reports in adolescents (12 to 17 years of age) were non-serious and included events known to be associated with nicotine products. No new safety concerns were noted.

As noted above, efficacy of NRT products has not been adequately studies in adolescents. We know, however, that use of tobacco products is one of the leading preventable causes of mortality and morbidity in the United States.[1] Smoking among adolescents presents issues with significant public health implications, since many adults smokers begin when they are young. Of the 2.4 million new smokers identified in 2006 (number of persons aged 12 and older who smoked cigarettes for the first time within the past 12 months), 61.2% (1,468,800 individuals) were under age 18.[2] Clearly educating adolescent smokers about the consequences of smoking

and supporting them in their effort to quit the habit should be prominent features of any public health campaign. NRTs, given their favorable safety profile and longer marketing history relative to bupropion or varenicline, would be better candidates as pharmacotherapy for use in conjunction with counseling to help adolescent smokers quit smoking. Though the studies reviewed do not provide convincing evidence of efficacy, there is some evidence that NRTs may be useful in certain 'older' adolescents – particularly those who may be more addicted or heavier tobacco users.

Since there is no evidence of an increased safety concern for use of this product in adolescents and the pharmacokinetic profile is similar to that of adults, it seems reasonable and appropriate to change the labeling to state that efficacy has not been established and that use by those < 18 years of age should be discussed with a physician. (Current labeling states "if you are under 18 years of age, ask a doctor before using.") There may be select patients for whom the product is appropriate and this will allow use of the product in a safe manner.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No special postmarketing risk management activities are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

No additional requirements are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Nicorette nicotine polacrilex lozenge was approved for OTC marketing in 2002. The lozenges are marketed in doses of 2 mg and 4 mg with the indication to "reduce withdrawal symptoms, including nicotine craving associated with quitting smoking." Nicorette lozenges are available in original, mint, and cherry flavors.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently several therapies available for smoking cessation. In addition to Nicorette lozenge, nicotine polacrilex is available as a gum and nicotine is also available as a slow release patch, a nasal spray, and an oral inhalation device. The currently marketed NRT products are shown in Table 1. Nicotine nasal spray and nicotine inhaler are prescription products. The lozenge and the gum are available in several flavors and are over-the-counter (OTC) products. Nicotine patches as well as nicotine polacrilex gum and lozenges are available in generic formulations. There are two other prescription products, varenicline and bupropion, that are also approved therapies for smoking cessation.

Table 1: Approved NRT Products in the United States

NRT Product	Maximum Daily Dose	Application Number	Marketing Status
ProStep nicotine patch	22 mg/day	NDA 19-983	Discontinued
Habitrol nicotine patch	21 mg/day	NDA 20-076	OTC
Nicoderm CQ nicotine patch	21 mg/day	NDA 20-165	OTC
Nicorette nicotine polacrilex gum	96 mg/day	NDA 18-612 & 20-066	OTC
Nicorette nicotine polacrilex lozenge	80 mg/day	NDA 21-330	OTC
Nicorette nicotine polacrilex mini-lozenge	80 mg/day	NDA 22-360	OTC
Nicotrol nicotine oral inhaler	64 mg/day	NDA 20-714	Prescription
Nicotrol nicotine nasal spray	20 mg/day	NDA 20-385	Prescription

2.3 Availability of Proposed Active Ingredient in the United States

Nicotine replacement products have been available in the United States since 1984. Nicotine polacrilex was initially approved in the gum form as a prescription product in 1984 and switched to an OTC product in 1996. It is currently marketed in several flavors. Nicotine as a slow release patch formulation was approved as a prescription product in 1991 and was switched to OTC marketing in 1997. Commit lozenges (now known as Nicorette) were approved for OTC marketing in 2002 and are also available in several flavors. Nicorette mini-lozenges (a smaller version of the nicotine polacrilex lozenges) were approved for OTC marketing in 2009. Nicotine replacement is also available by prescription as a nasal spray and an inhaler.

2.4 Important Safety Issues with Consideration to Related Drugs

Currently, OTC sale of products intended to aid smoking cessation is restricted to consumers aged 18 years and older. Consumers are advised not to smoke cigarettes while using nicotine replacement products.

Consumers with hypertension, diabetes, or cardiovascular disease are instructed to discuss nicotine replacement therapy (NRT) use with their physicians; however, NRTs are believed to be safer than cigarettes. While pregnant women or those who are nursing are also advised not to smoke, NRT use in these women remains a controversial topic, as prenatal or neonatal nicotine exposure to nicotine remains a concern.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

NDA 21-330 was approved on October 31, 2002. At the time of approval, GSK was granted a deferral (until October 31, 2007) for submission of pediatric studies for children ages 10 to 17 years and a waiver for pediatric study requirements for children under age 10 years.

In the early 1990s, FDA implemented voluntary measures to encourage pediatric studies in an effort to provide more informative pediatric labeling for new drug products. These efforts culminated in the 1997 Food and Drug Administration Modernization Act (FDAMA) that included a pediatric exclusivity provision. This provision was reauthorized in 2002 and extended through 2007 as the Best Pharmaceuticals for Children Act (BPCA).[3] However, due to the lackluster results of voluntary pediatric provisions, FDA published a proposed regulation in 1997 that, for the first time, required manufacturers of new drugs and biological products to conduct pediatric studies in some circumstances. This rule was finalized on December 2, 1998, and the first studies were required to be submitted starting December, 2000.[4]

On December 4, 2000, the Association of American Physicians and Surgeons (AAPS), and two other consumer groups – Competitive Enterprise Institute (CEI) and Consumer Alert – jointly filed suit to challenge the Agency's authority in enforcing this Pediatric Rule.[5] On October 17, 2002, the U.S. District Court for the District of Columbia ruled against FDA.[6] At the time of approval for NDA 21-330, the Agency had not decided whether to appeal this ruling or to ask for a stay of the court's order. Therefore, the approval letter for NDA 21-330 acknowledged to GSK that the FDA had been barred from enforcing the Pediatric Rule by the Federal Court. Further, the approval letter contained "a description of the pediatric studies would be required under the Pediatric Rule, if the Pediatric Rule remained in effect and/or were upheld on appeal." The letter stated that FDA would notify GSK whether NDA 21-330 would be subject to the requirements of the Pediatric Rule, pending resolution of the lawsuit.[7] However, it appears that FDA did not explicitly notify GSK of the final outcome of the lawsuit or confirm with GSK that the Pediatric Rule remained in effect. It also appears that GSK did not seek FDA feedback regarding pathway to address pediatric rule following resolution of the law suit.

The scope of FDA's authority to require pharmaceutical manufacturers to conduct appropriate pediatric clinical trials was finally settled when Congress passed the Pediatric Research Equity Act (PREA). PREA was signed into law on December 3, 2003.[1]

GSK submitted results of Study S1330074, "A Pharmacokinetic and Safety Study of (b) (4) Nicotine Replacement Therapy Formulations in Adolescent Smokers, " on August 20, 2007. This open-label, dose escalation study sought to characterize the pharmacokinetic (PK) profiles and evaluate safety of three nicotine replacement therapy formulations (patch, gum, and lozenge) in adolescent smokers aged 10 to 17. With study S1330074, GSK intended to claim satisfactory completion of the requirements under the Pediatric Research Equity Act (PREA). In this study, 45 subjects aged 13 to 17 were able to complete the lower doses of the three formulations (2 mg lozenge, 14 mg patch, and 2 mg gum) and 37 subjects completed the higher doses of each formulation (4 mg lozenge, 21 mg patch, and 4 mg gum). The incidence of nausea appeared to be higher in these adolescent subjects when compared to the adults who were enrolled in the efficacy/safety studies conducted to support approval of these NRT formulations. Study S1330074 was reviewed by DNCE and the Pediatric Maternal Health Staff (PMHS); both concluded the findings were not adequate to satisfy PREA requirements.

On August 19, 2008, FDA notified GSK that the terms of PREA were not fulfilled. The letter stated: "The fact that [GSK was] not interested in pursuing approval of an OTC pediatric indication does not relieve [the sponsor] of this commitment under PREA. The pharmacokinetics study in the August 20, 2007 submission does not satisfy this commitment because it does not adequately assess the safety and efficacy of Commit in children ages 10 – 17 years."[8]

GSK met with FDA on February 4, 2009 to discuss the path forward to address the PREA requirements. FDA advised that in order to meet PREA obligations, GSK can either conduct a de novo clinical efficacy study using the lozenge or submit the full published literature reports to support their position that the required studies under PREA have been completed. GSK expressed their interest in using published literature alone to demonstrate lack of NRT efficacy in adolescents. GSK then agreed to submit literature review and analysis for FDA to determine whether PREA has been addressed.[9]

GSK submitted a comprehensive review of published literature on adolescent smoking cessation as a General Correspondence on February 19, 2010. In the July 15, 2010 response, FDA informed GSK that given the extent of clinical data, the submission would need to be an efficacy supplement in order to fulfill the terms of PREA. On March 25, 2011, GSK submitted an efficacy supplement containing the identical review of literature. The application did not contain any proposed labeling change to reflect known pediatric data, despite GSK's assertion that NRTs have not been shown to be effective in adolescents. On April 15, 2011, GSK proposed including the following labeling: "If you are under 18 years of age, ask a doctor before use. (b) (4) (b) (4)" The submission underwent administrative review and FDA notified GSK on May 19, 2011 that the application was unacceptable without payment of the appropriate user fee. GSK paid the required fee on August 9, 2011 and this became the effective submission date.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality of the initial submission was poor and materially incomplete, necessitating repeated requests from FDA for additional information. In the March 25, 2011 cover letter accompanying this supplemental application, GSK noted that data included in this submission "were either provided by the investigators to GSK directly or by letter of authorization from the sponsor. GSK did not conduct these studies nor had any role in the generation of the data. GSK is relying upon the data as provided by the investigator directly or by letter of authorization and did not analyze the data or reassess the conclusions drawn by the investigators." Having made this statement, GSK failed to provide an Integrated Summary of Safety in the initial application. The filing letter sent to the applicant on October 11, 2011 included a request for an Integrated Summary of Safety. A second request was made on November 23, 2011 and the safety summary was not provided until January 31, 2012, almost six months into the review cycle.

In addition, the submitted Drug Facts label failed to conform to the format needed for labeling review. Revised labeling was provided on February 10, 2012, more than six months into the review cycle.

3.2 Compliance with Good Clinical Practices

Only one clinical study (S1330074) is included in this application. The final study report states this pharmacokinetic study was conducted under the supervision of an Institutional Review Board and in accordance with the Declaration of Helsinki, the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice, and FDA Good Clinical Practice Regulations (21 CFR; parts 50, 56, and 312).

3.3 Financial Disclosures

In the January 31, 2012 amendment, GSK states that the disclosure requirement does not apply to any investigator involved in study S1330074.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no new CMC issues relevant to this supplemental application.

4.2 Clinical Microbiology

There are no outstanding clinical microbiology issues.

4.3 Preclinical Pharmacology/Toxicology

No new nonclinical studies were conducted to support this efficacy supplemental application.

4.4 Clinical Pharmacology

Five pharmacokinetic studies conducted in healthy adults were submitted in the original NDA:

Table 2: Clinical Pharmacology Studies to Support Original NDA 21-330 Submission

Study	Objective	Treatment
N98001	Pilot single-dose bioavailability	2 mg lozenge vs. 2 mg gum
N96016	Pilot single-dose bioavailability	4 mg lozenge vs. 4 mg gum
S1410090	Single-dose bioavailability, assessing effects of misuse	4 mg lozenge • Labeled use (not chewed or swallowed) • Chewed & swallowed • Chewed, retained in the mouth, then swallowed
S1410091	Multiple-dose bioavailability	2 & 4 mg lozenge every 90 minutes x 9 2 & 4 mg gum every 60 minutes x 13
S1410092	Bioequivalence	3 mg lozenge vs. 4 mg gum

Pharmacokinetic data from these five studies was extracted from the original clinical pharmacology review[10] showing peak serum concentration was achieved approximately one hour after dosing, regardless of the lozenge dose. These results are shown in Table 3.

Table 3: Plasma Nicotine PK Profile (Adults) following a Single Dose of NRT Products

Study	Product	T_{max} (hr)	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng*hr/ml)
N98001	2 mg lozenge	1.0	4.4	14.1
	2 mg gum	0.8	4.0	11.3
N96016	4 mg lozenge	1.1	10.8	44.0
	4 mg gum	0.9	10.0	34.6
S1410090	4 mg lozenge, used as directed	1.0	7.8	30.8
	4 mg lozenge, chewed & swallowed	1.3	5.7	24.6
	4 mg lozenge, chewed, retained, & swallowed	1.4	6.8	28.7
S1410091	2 mg lozenge x 9 doses	0.5	12.7	31.8*
	4 mg lozenge x 9 doses	0.7	26.0	67.3*
	2 mg gum x 13 doses	0.6	16.1	41.3*
	4 mg gum x 13 doses	0.5	32.2	87.8*
S1410092	3 mg lozenge	0.9	7.1	25.7
	4 mg gum	0.8	8.0	25.4

* Values presented are AUC_{0-T}

GSK conducted study S1330074 to assess the pharmacokinetic parameters of NRT formulations in adolescents age 13 to 17 years. Three different NRT formulations were studied (gum, lozenge, and patch) with two doses of each product. The PK results are summarized in Table 4.

Table 4: Plasma Nicotine PK Parameters (Adolescents) Study S1330074

Product		T_{max} (hr)	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng*hr/ml)
Patch	14 mg	5.0	16.4	227.6
	21 mg	4.6	24.3	327.8
Lozenge	2 mg	1.1	5.4	21.4
	4 mg	1.2	11.1	44.5
Gum	2 mg	0.6	6.2	19.7
	4 mg	0.7	10.8	34.9

Reviewer Comments: It is difficult to compare data across studies – however – the pharmacokinetic parameters following single-dose exposure to 2mg and 4mg lozenges appear to

be comparable in adults (Table 3) and adolescents (Table 4). The Clinical Pharmacology reviewer agrees that systemic exposure to nicotine for adults and adolescents age 13 – 17 is generally comparable for the same product formulation at the same dose.

5 Sources of Clinical Data

Clinical data presented in this supplemental application includes the following:

- Study S1330074, a dose-escalating, pharmacokinetic evaluation of nicotine patch, gum, and lozenge formulations in 45 adolescents 13 to 17 years of age
- GSK's worldwide clinical safety database for nicotine patch, gum, and lozenge from October 31, 2007 to October 30, 2011
    - The search focused on adolescents younger than 18 years of age
- Literature provided by the applicant, consisting of eight publications originating from seven clinical trials in adolescent smokers

There have been a number of studies on the use of NRT in adolescent smoking cessation. The sponsor has included eight publications summarizing seven randomized, double-blind, controlled studies (six placebo-controlled, one active-controlled). Two of these trials were not designed specifically to explore the efficacy of NRT for smoking cessation and will be discussed only in the safety section of this review. Other published reports, including two randomized, open-label, controlled trials and two uncontrolled trials were also included and will also be discussed further in the safety section of this review. The five published reports and one clinical trial reviewed for efficacy and safety are shown in Table 5.

5.1 Tables of Studies/Clinical Trials

Table 5: Clinical Studies and Trials Reviewed for Efficacy and Safety

Study	Design	N	Duration of treatment	Age (years)	Treatment	Other interventions
GSK S1330074	Pharmacokinetic study: two-period, dose-escalation	Period 1: 45	Single-dose	13-17	Lozenge 2 mg Patch 14 mg Gum 2 mg	None
		Period 2: 37	Single-dose		Lozenge 4 mg Patch 21 mg Gum 4 mg	
Roddy 2006	Published report; R, DB, PC study	98	6 weeks	12-20	Patch Placebo	Behavioral counseling
Moolchan 2005	Published report; R, DB, PC	120	12 weeks	13-17	Patch Gum Placebo	Cognitive behavioral therapy
Wold 2005	Public Presentation; R, DB, PC	50	10 weeks	13-18	Patch Placebo	Not Reported
Stotts 2003	Published Report; R, DB, PC	303	6 weeks	14-19	Patch Placebo Usual care	Group Behavioral intervention classes vs. 5-10 minute counseling and f/u phone call
Hanson 2003	Published Report: R, DB, PC	100	10 weeks	13-19	Patch Placebo	Cognitive behavioral therapy

5.2 Review Strategy

Assessment of product efficacy will be completed by reviewers in the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP). The pharmacokinetic data (summarized in section 4.4) will be evaluated by reviewers in the Division of Clinical Pharmacology. This DNCE review will focus on the clinical safety perspective of data submitted in this supplemental application. The single clinical study conducted in adolescents (S1330074) has previously been reviewed by FDA. These results are summarized in section 5.3. A summary of the studies from published literature is also included in this section. The safety information obtained from GSK's search of their worldwide clinical safety database is discussed in section 8 (Postmarketing Experience). A summary of the safety results from the GSK study and the published literature reports is presented in section 7.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study S1330074

Study S1330074, entitled "A Pharmacokinetic and Safety Study of (b) (4) Nicotine Replacement Therapy Formulations in Adolescent Smokers," has already been reviewed by FDA. (Please refer to the DNCE clinical review dated March 11, 2008 and the consult report by the Pediatric and

Maternal Health Staff PMHS, dated April 3, 2008 for additional detail.) This was a single-center, single-dose, open-label, dose escalation study. (b) (4) three NRT formulations, nicotine patch, gum, and lozenge, were assessed in this study.

This study was conducted by a single investigator between August 2000 and December 2001. It enrolled healthy adolescent smokers who either smoked more than 10 cigarettes per day (CPD) during the past three months or reported the use of tobacco products. The doses of NRT medication selected for use in this study were the labeled adult doses for all three formulations (nicotine lozenge, nicotine transdermal patch and nicotine gum). Subjects were given the lower dose of the assigned formulation according to specific instructions and blood samples were obtained over a 12-hour period (session 1). If the lower dose did not raise safety concerns, the subject was scheduled for session 2 at which time the higher dose of the assigned formulation was administered. As in session 1, blood samples were also obtained over 12-hours post-dose in session 2. The dose-escalation schedule for the three NRT formulations studied is presented in Table 6 below.

Table 6: Dose Escalation Schedule, Study S1330074

Cohort	Treatment	Dosage	
		Session One	Session Two
1	Nicotine Lozenge	2 mg	4 mg
2	Nicotine Transdermal Patch	14 mg	21 mg
3	Nicotine Gum	2 mg	4 mg

Initially a total of 72 subjects were planned to yield 48 evaluable subjects (b) (4)
(b) (4)
At least three subjects in each formulation group were to be in the age range of 10 to 14 years. However, because of the difficulty in finding young smokers, the subjects recruited for the younger smoker group were either 13 or 14 years old. Several inclusion and exclusion criteria were relaxed in order to increase recruitment of subjects.

Pharmacokinetic Results:
A total of 45 subjects (21 males and 24 females) aged 13 to 17 years were enrolled and completed session 1. A total of 37 subjects completed session 2. Eight subjects were enrolled into the study twice, and with each enrollment entered into a cohort and assigned a new subject number. As shown in Tables 2 and 3 above, the pharmacokinetic parameters for adolescents and adults are similar after single-dose administration of the tested nicotine replacement products. It was noted that Cmax values for the adolescents studied were higher than those in adults, which may explain the increase in nausea observed in this study.

Investigator Conclusion
The study investigator concluded that the three formulations of NRTs used in the study were well-tolerated in these adolescent subjects. The nature of the adverse events experienced was consistent with the known adverse event profile of each formulation. There were no unexpected adverse events observed with the administration of nicotine formulations in these adolescent smokers.

DNCE Reviewer Conclusion
This small study in subjects aged 13 to 17 suggests that adolescents may tolerate these NRT formulations studied. However, significant proportions of study subjects reporting nausea after receiving the treatment (e.g., 31% after receiving 2 mg lozenge, 39% after receiving the 4 mg lozenge) suggest that the adult dosages in NRT may be too high for the pediatric population. Additionally, the Sponsor has not adequately addressed the adolescent population. The approval of NDA 21-330 specified that pediatric studies be conducted for the 10 to 17 age group; no data was included for the 10 to 12 age group. Because of the small sample size and study design, the submitted safety evaluation is insufficient to conclude that nicotine replacement products in these formulations studied (lozenge, patch, and gum) are safe for use in the adolescent population aged 10 to 17. Therefore, results from this study would not be adequate to effect labeling change to expand the covered population to children aged 10 to 17.

Pediatric and Maternal Health Staff (PMHS) Conclusion
The study was also reviewed by PMHS to examine the adequacy of this pediatric postmarketing safety and pharmacokinetic study in addressing GSK's PREA obligation under NDA 21-330. In her consult dated March 4, 2008, Dr. Amy Taylor agreed that GSK failed to satisfy the PREA requirements with a pediatric study of this scale. The Sponsor's stated disinterest in pursuing OTC pediatric indication for Commit lozenges does not relieve them of this commitment.

5.3.2 Roddy et al. (2006)[11]

This was a randomized, double-blind, placebo-controlled study in 98 adolescents comparing six weeks of treatment with the nicotine patch or a placebo; all subjects received behavioral counseling weekly in either one-on-one session or small group sessions. To be included in the study, subjects had to be 12 to 20 years of age, be a regular smoker (greater than 1 cigarette per day (CPD) or less than 1 CPD but past or anticipated withdrawal) with carbon monoxide validation (>5ppm), with no medical contraindications. Subjects were excluded if they were: 12-14 years of age or greater than 14 years of age but not competent to consent or parents were unable or unwilling to consent; a self-reported non-smoker; allergic to sticking plaster; or pregnant or at risk of becoming pregnant.

Only eight subjects (three active and five placebo) completed the full six weeks of treatment. Over half did not attend follow-up after the initial screening and recruitment. Two subjects withdrew because of adverse events (one active and one placebo patient); two withdrew because they had quit smoking, one because they perceived the patches to be ineffective; and 22 changed

their minds about quitting. The remaining 63 did not attend future follow-up (and thus were assumed to still be smoking).

At week 4, slightly more active patch users (vs. placebo patch users) were abstinent (5 subjects vs. 2 subjects); no subjects were abstinent at week 13. Due to the very high attrition rate, however, it is difficult to assess efficacy of the patch in this study. This study also included subjects smoking < 1 cigarette per day though the median number of cigarettes smoked per day was 10.

Reviewer Comment: The extremely high attrition rate makes this study essentially impossible to interpret. Additionally, subjects could be enrolled even if they smoked < 1 CPD; this seems illogical. I don't believe the data from this study contributes any additional clinically useful efficacy information.

5.3.3 Moolchan et al. (2005)[12]

This was a randomized, double-blind, placebo-controlled study in 120 adolescents comparing 12 weeks of treatment with 1) nicotine patch and placebo gum (n=34), 2) nicotine gum and placebo patch (n=46), or 3) placebo patch and gum (n=40). All participants received cognitive behavioral therapy (CBT) with a 45 minute group session led by a trained social worker at the end of each treatment visit. The objective of the study was to assess the safety and efficacy of the nicotine patch and gum for adolescents who want to quit smoking. The primary analysis, for which the study was powered, was smoking reduction. The study also assessed measures of cessation (point prevalence abstinence, prolonged abstinence), as well as safety.

Adolescents were eligible for the trial if they: were 13 to 17 years of age, were in good general health, had smoked ≥10 CPD for at least 6 months, had a minimum score of 5 on the Fagerström Test of Nicotine Dependence (FTND), and were motivated to quit smoking. Adolescents were excluded if they were pregnant or lactating, had chronic skin conditions, used other tobacco products, or currently used (within 30 days) other medications for smoking cessation (e.g., NRT, bupropion). The mean age was 15.2 $\pm$ 1.33 years; mean CPD was 18.8 $\pm$ 8.56. Subjects using psychotropic medications not prescribed for smoking cessation were included.

Of the 120 randomized subjects, 53 completed the study (19 using active gum, 18 using active patch and 16 using placebo). No details of the reasons for dropping out of the trial are given though the authors state "our clinical impression was that adverse events did not affect retention substantially."

This study found that significantly higher prolonged abstinence rates were achieved in the nicotine patch group compared to the placebo group. The difference between the gum and placebo was not significant. The prolonged abstinence rate at 12 weeks was 17.7%, 6.5% and 2.5% in the patch, gum, and placebo groups, respectively (patch vs. placebo, p=0.043; gum vs. placebo, p=0.62). This trial was powered to detect a significant difference in cigarette reduction, rather than abstinence, and as a result, there are wide confidence intervals associated with the

effects. There was a more than 80% reduction in CPD in all treatment groups but neither biomarker (expired CO or saliva thiocyanate levels) decreased, so it is not clear that smoking truly decreased. The authors theorize that the teens may have reported their cigarette consumption inaccurately or perhaps deeper inhalation may have affected the measurements.

Reviewer Comment: Though it is common in studies of this nature, the high drop-out rate makes interpretation difficult. This study seems to indicate that some adolescents who are more highly addicted and motivated to quit may benefit from use of NRT. The authors believe additional studies using flavored NRT products and with a primary endpoint of cessation, rather than reduction, should be undertaken. They also believe that developmentally appropriate behavioral and counseling support is important for adolescents and that creative strategies are needed to retain adolescents in future trials. I believe the authors' suggestions are reasonable.

5.3.4 Wold et al. (2005)[13]

This was a randomized, double-blind, placebo-controlled trial of nicotine patch vs. placebo in 50 adolescent smokers. The subjects enrolled were generally healthy, smoked > 10 CPD, had a CO level $\geq$ 10 parts per million (ppm), and were not taking bupropion. All of the subjects were selected from those enrolled in a day treatment program for adolescents with serious conduct and/or substance abuse problems. There were 50 subjects randomized to treatment; 39 (78%) completed a one-month follow-up assessment and 34 (68%) completed the 10-week protocol. The mean age of the subjects was 16.2 for the active patch group and 16.0 for the placebo group. The mean Fagerstrom dependence score was 7.6 for the active patch group and 7.3 for the placebo group.

The cessation rates were the same for patch and placebo (4%) during the study. However, there was a difference in the number of subjects who reported greater than an 80% reduction in daily cigarette use (patch: 72% vs. placebo: 48%, p=0.07) and a significant difference in the mean number of cigarettes per day reduction (15 cigarettes vs. 8 cigarettes, patch vs. placebo, p=0.02) among subjects who completed the study. The difference in CO reduction (patch vs. placebo, 8ppm vs. 4ppm, p=0.09) was not significant. The investigator concluded that the nicotine patch may be a feasible option when combined with behavioral therapy.

Reviewer Comment: This study is presented in abstract form only. This study population consisted of 'older' and 'more highly addicted' adolescents. The results do not indicate a difference in the cessation rate for those using the patch though the reported number of cigarette smoked per day did decrease. The clinical significance of this is not clear.

5.3.5 Stotts et al. (2003)[14]

This was a randomized, double-blind (patch groups only), placebo-controlled study comparing usual care, placebo patch, or active nicotine patch treatment in 303 adolescent males who were current users of spit tobacco (ST). All subjects received behavioral intervention classes. The primary objective was examination of the effects of nicotine patch on ST cessation but the study

also examined cigarette abstinence at the one-year follow-up. Subjects received treatment for six weeks and follow-up for one year. Of the adolescents eligible for inclusion in the study 105 were randomized to treatment with usual care (5-10 minutes counseling followed by a phone call 2 weeks later), 98 were in the active nicotine patch group, and 100 in the placebo patch group. A total of 98 adolescents (32%) completed the trial; 25 in the usual care group, 33 in the active patch group, and 40 in the placebo patch group. There were three reported withdrawals due to adverse events (two reported headaches, one a "hyperreaction").The mean age for the usual care and active patch groups was 17; for the placebo patch group it was 16. Over 40% of the subjects were high school seniors and over 65% also used cigarettes.

This study found lower abstinence rates at one year for both usual care and the active patch when compared to placebo (11.4%, 17.3%, and 25.0%, respectively, for ST; 14.3%, 12.2%, and 23.0%, respectively, for cigarettes). End of treatment abstinence rates are provided for ST only and were significantly lower for usual care (3.8%) compared to either the active (31.6%) or placebo patch (29.0%). Abstinence rates were similar for the active and placebo patch post-intervention.

Reviewer Comment: This study included only males, mostly in the older adolescent range, even though subjects could be as young as 14 years of age. Additionally, the focus was spit tobacco, not cigarettes, though many of the subjects used both forms of tobacco. The study does not add significantly to the support of efficacy for the nicotine patch in this population.

5.3.6 Hanson et al. (2003)[15]

This was a randomized, double-blind, placebo-controlled study of 100 adolescent smokers, age 13 – 19 years comparing nicotine patch and placebo treatment. All participants received individual cognitive behavioral therapy and participants earned 'rewards' for measurable documentation of abstinence during the trial. The primary objective was to examine the effects of the patch on nicotine withdrawal symptoms and secondarily, to evaluate the effectiveness in helping adolescents quit smoking. Subjects were ages 13 – 19, current smokers of at least 10 CPD for at least six months, not using other tobacco products more than once a week, motivated to quit, and not currently using NRT. Exclusion criteria were contraindications to nicotine patch therapy or taking psychoactive medications (except to treat ADD/ADHD) in the last six months. The mean age of participants was 16.8 $\pm$ 1.5 years and the mean CPD was 16.3 $\pm$ 4.9. Most (80%) of the subjects reported at least one previous quit attempt.

The overall smoking cessation rates at week 10 were similar in the active and placebo group and there was no significant difference in overall time of abstinence (p=0.31). However, only the nicotine patch significantly reduced the severity of craving and withdrawal symptoms in the two weeks following the quit attempt (p=0.011 and p=0.025, respectively). Among study completers who did not abstain for at least 9 weeks during treatment, there was a significant reduction in both CO and CPD but no comparison between active and placebo is provided. Salivary cotinine levels differed by treatment group at 1 week post quit, the difference diminished over time. Approximately half (53%) of the randomized subjects completed the study; 25 subjects

randomized to patch and 28 randomized to placebo. Reasons for drop outs during the trial are not provided; however, no subject discontinued the study due to an adverse event.

Reviewer Comment: This study population also consisted of 'older' and 'more highly addicted' adolescents. As with most of these studies, the drop-out rate was high. The results do not indicate a difference in the cessation rate for those using the patch though the reported number of cigarette smoked per day did decrease for both groups. The clinical significance of this is not clear.

6 Review of Efficacy

Efficacy Summary

Efficacy of Nicorette lozenge in the adult population was established in the pivotal placebo-controlled, efficacy and safety trial (S1410043) involving 1818 subjects in the original application to NDA 21-330. Additional efficacy support relied in part on reference to efficacy findings for Nicorette gum. GSK cites literature to support their conclusion that NRTs in general, have not been shown to be effective as smoking cessation aids in adolescent smokers. It is not clear this conclusion can be validated, given the numerous design flaws noted in the submitted literature reports. A complete review of efficacy was conducted by the Division of Anesthetic, Analgesic, and Addiction Products (DAAAP).

While the literature reports submitted do not clearly support the sponsor's conclusion that NRTs are ineffective smoking cessation treatment for the adolescent population, the reports do help identify the difficulties associated with conducting adequate and well-controlled trials that would definitively resolve this issue including:

- Difficulty recruiting: While most of the studies, including the PK study GSK conducted, attempted to recruit younger subjects, most participants were ages 14 or older. Enrolling younger adolescents for these studies is very difficult. This may be because young adolescents 'experimenting' with tobacco use are not really addicted. It is also possible that obtaining parental consent is challenging for this age group or that the parents may not be aware their child is smoking. Whatever the reasons, the difficulty in recruiting an adequate number of subjects into these studies was demonstrated by multiple researchers as well as the sponsor.
- High attrition rate: Even when the investigators were successful in recruiting subjects, the drop-out rates were very high – usually > 50%. There were several different study designs used and no specific method seemed to be more successful for retaining participants. Some investigators used 'reward' systems, but this was not particularly helpful.
- Difficulties of Study Design/Compliance: This is particularly challenging for NRT products that are meant for 'as needed' use. Most of the adolescent subjects are students and administering a medication to a student on an 'as needed' basis is very difficult. The reports included in this application were primarily studies conducted using the nicotine patch which is only applied once a day and circumvents this challenge. Unfortunately, other problems

with the studies prevented concluding that the patches were efficacious for smoking cessation therapy in this population. None of the literature reports submitted included a trial of the nicotine lozenge.

In summary, the data included in this submission does not support efficacy of NRTs for smoking cessation in the adolescent population. Despite the many attempts by multiple investigators, there have not been adequate studies conducted to state whether NRT products are or are not effective in this age group.

Reviewer Comment: The data included in this application is not adequate for determining the efficacy of NRTs for smoking cessation in the adolescent population. However, as noted above, completing well controlled efficacy studies in this population is probably not possible.

7 Review of Safety

Safety Summary

The available safety data show no evidence of a safety concern for the use of NRT products in the adolescent population. The PK study (S1330074) is the only study included in this application in which the nicotine lozenge was administered. The most common adverse events reported were nausea, pharyngitis, eructation and anemia. There were no serious adverse events. The other reports are from published literature studies. The NRTs administered in these studies were the nicotine patch (ten reports), nicotine gum (two reports), and nicotine nasal spray (one report). Cutaneous reactions and headaches were the most common complaints. The general pattern of adverse events was similar to the known results from studies in adults. No new safety issues were identified and there was no evidence of any significant safety concerns specifically associated with administration of NRT products to adolescents. Table 7 summarizes the formulations used, ages and number of subjects exposed, extent of exposure for each reviewed study.

Table 7: Summary of Adolescent Safety Data

Study	Design	N (enrolled)	Duration of Treatment	Age (years)	Treatment	Other interventions
GSK S1330074	PK, 2 period; dose escalation	1: 45 2: 37	Single-dose	13-17	1: Lozenge 2 mg Patch 14 mg Gum 2 mg 2: Lozenge 4 mg Patch 21 mg Gum 4 mg	None
Roddy 2006	R, DB, PC	Total: 98 Active: 49 Placebo: 49	6 weeks	12-20	Patch: 15/10/5 mg Placebo	Behavioral counseling
Moolchan 2005	R, DB, PC	Total: 120 Patch: 34 Gum: 46 Placebo: 40	12 weeks	13-17	Patch: 21/14 mg Gum: 4/2 mg Placebo	Cognitive behavioral therapy
Wold 2005	R, DB, PC	50 (breakdown not given)	10 weeks	13-18	Patch (dose not given) Placebo	Not reported
Stotts 2003	R, DB, PC	Total: 303 Patch: 98 Placebo: 101 Usual care: 105	6 weeks	14-19	Patch: 21/14/7 mg OR 14 /7 mg Placebo Usual Care	Group Behavioral intervention classes vs. 5-10 minute counseling and f/u phone call
Hanson 2003	R, DB, PC	Total: 100 Active: 50 Placebo: 50	10 weeks	13-19	Patch: 21/14/7 mg OR 14 /7 mg Placebo	Cognitive behavioral therapy
Killen 2001	R, DB, PC	Total: 89 Placebo: 46 Active: 43	Single-dose	13-18	Patch 15 mg	None
Killen 2004	R, DB, AC	211 (all received patch)	Patch:8 weeks (plus bupropion or placebo)	15-18	Patch: 21/14/7 mg OR 14 /7 mg	Group counseling
Rubinstein 2008	R, open-label	Total: 40 Spray: 23 Therapy alone: 17	6 weeks	15-18	Nicotine nasal spray NTE 40 doses/day (each dose ~ 1 mg nicotine) vs. therapy alone	All received Group counseling
Hanson 2008	R, open-label	Total:103 Patch: 34 Gum: 33 Placebo: 36	4 weeks	13-19	Nicotine gum: 2/4 mg or Nicotine patch: 7/14/21 mg (dose based on CPD)	Cognitive behavioral therapy
Hurt 2000	R, open-label	Total: 101 (all received patch)	6 weeks	13-17	Nicotine patch 15 mg	Minimal behavioral therapy
Smith 1996	R, open-label	Total: 22 (all received patch)	8 weeks	13-17	Nicotine patch 22 mg/day x 6 weeks, 11 mg/day x 2 weeks	Weekly behavioral counseling

7.1 Methods

To evaluate safety, GSK included the findings from the PK study (Study S1330074) and from five randomized, double-blind, placebo-controlled efficacy studies found in published literature. In addition, the other studies from published literature referenced in section 5 are included. These studies included adolescent subjects and provide additional safety data.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety results from each source are summarized below.

Study S1330074 Safety Results
A total of 45 subjects (21 males and 24 females) aged 13 to 17 years were enrolled and completed session 1 of this study and 37 subjects completed session 2. Eight subjects were enrolled into the study twice. The doses of NRT medication selected for use in this study were the labeled adult doses for all three formulations (nicotine lozenge, nicotine transdermal patch and nicotine gum). Subjects were given the lower dose of the assigned formulation according to specific instructions and blood samples were obtained over a 12-hour period (session 1). If the lower dose did not raise safety concerns, the subject was scheduled for session 2 at which time the higher dose of the assigned formulation was administered. The dose escalation schedule is shown in Table 6 (Section 5.3.1).

A total of 61 adverse events (AEs) were reported by 30 (67%) of the 45 subjects dosed during session one (lower doses of each formulation). A total of 58 adverse events (AEs) were reported by 27 (69%) of the 39 subjects dosed during session two (higher doses of each formulation). Of the eight subjects who participated in two study arms, all were able to complete both dose-escalation sessions. Mild adverse events were experienced by seven of these subjects; one of the eight subjects did not report any adverse events. There were no deaths reported during the conduct of the study. The overall rates of AEs were similar between the low and high doses in each of the formulations.

The most commonly reported AEs were nausea, pharyngitis, eructation and anemia; only nausea, pharyngitis and eructation were deemed by the investigator to be treatment-related adverse events. All but one of the reported AEs were considered by the investigator to be mild or moderate in intensity; the only AE that was classified as severe was “throat burn” (reported by subject number 63 in the Nicorette 4 mg gum group). Two subjects were discontinued due to adverse events. They both reported nausea and vomiting, which were considered to have a highly probable relationship to the study medication. There were subjects who developed anemia during the study; this was believed to be due to the quantity of blood drawn during the study.

Reviewer Comment: This was a single-dose PK study so adverse event information is limited. There was some evidence of increased nausea but no serious or unexpected AEs were noted.

Roddy et al. (2006)[11]
This was a randomized, double-blind, placebo-controlled study in 98 adolescents (ages 12 to 20 years) comparing six weeks of treatment with the nicotine patch or a placebo; all subjects received behavioral counseling weekly in either one-on-one session or small group sessions. Only eight subjects completed the full six weeks of treatment.

Adverse events were higher in the active group but all were non-severe. Two patients withdrew due to adverse events; one using active drug and one using placebo. The most common AE was itching. The reported adverse events are shown in Table 8.

Table 8: Adverse Event Reports (Roddy et al.)

Adverse Event	Patch (n=49)	Placebo (n=49)
Itching	16 (32.7%)	7 (14.3%)
Rash	6 (12.2%)	3 (6.1%)
Pain/Paresthesia at patch site	6 (12.2%)	4 (8.2%)
Dizziness, nausea, or headache	2 (4.1%)	3 (6.1%)

Reviewer Comment: Only eight subjects completed the full treatment in this study making analysis difficult. There was an increase in reports of itching for subjects using the active patch but this is not unexpected for the nicotine patch.

Moolchan et al. (2005)[12]
This was a randomized, double-blind, placebo-controlled study in 120 adolescents (ages 13 to 17 years) comparing 12 weeks of treatment with 1) nicotine patch and placebo gum (n=34), 2) nicotine gum and placebo patch (n=46), or 3) placebo patch and gum (n=40). Of the 120 randomized subjects, 53 completed the study (19 using active gum, 18 using active patch and 16 using placebo). No details of the reasons for dropping out of the trial are given though the authors state "our clinical impression was that adverse events did not affect retention substantially."

A significant increase over placebo was noted for sore throat, hiccups, shoulder/arm pain, pruritis, and erythema. The reported adverse events are shown in Table 9.

Table 9: Adverse Event Reports (Moolchan et al.)

Adverse Event	Overall	Patch (476 person-wks)	Gum (552.1 person-wks)	Placebo (439.9 person-wks)
Pruritus	130	44*	61*	25
Erythema	111	49*	39	23
Headache	86	24	26	36
Fatigue	67	15	20	32
Viral infection	63	14	30	19
Insomnia	43	13	17	13
Cough	32	9	15	8
Nausea	31	10	10	11
Jaw pain	30	10	12	8
Anxiety	26	6	13	7
Sore throat	24	3	18*	3
Hiccups	22	4	14*	4
Dyspepsia	22	4	10	8
Shoulder/arm pain	18	15*	0	3
Dizziness	15	3	3	9

*p<0.05 vs. placebo

Reviewer Comment: An increase in itching and erythema are noted in subjects using the nicotine patch. There was also increased itching noted in the gum users – the reasons for this are not clear. Use of the gum was also associated with an increase in sore throat and hiccups. None of the described adverse events are unexpected or new findings for the NRT products being administered in this study.

Wold et al. (2005)[13]
This was a randomized, double-blind, placebo-controlled trial of nicotine patch vs. placebo in 50 adolescent smokers. Of the 50 subjects randomized to treatment; 39 (78%) completed a one-month follow-up assessment and 34 (68%) completed the 10-week protocol. The mean age of the subjects was 16.2 years for the active patch group and 16.0 years for the placebo group.

This study is presented in abstract form only. There were no serious AEs reported and no subjects withdrew due to an adverse event. The most common AEs were redness, itching, burning, and headache. The reported AEs are shown in Table 10.

Table 10: Adverse Event Reports (Wold et al.)

Adverse Event	Patch (%)	Placebo (%)
Redness, Itching, Burning	80%	64%
Headache	48%	44%
Arm pain	40%	16%
Muscle pain	36%	20%
Insomnia	28%	36%
Tiredness	24%	36%
Strange dreams	28%	44%

Reviewer Comment: Use of the patch was associated with increased itching and burning. This is not a new or unexpected finding.

Stotts et al. (2003)[14]
This was a randomized, double-blind (patch groups only), placebo-controlled study comparing usual care, placebo patch, or active nicotine patch treatment in 303 adolescent males who were current users of spit tobacco. Subjects received treatment for six weeks and follow-up for one year. One hundred five subjects were randomized to treatment with usual care (5-10 minutes counseling followed by a phone call 2 weeks later), 98 were in the active nicotine patch group, and 100 in the placebo patch group. A total of 98 adolescents (32%) completed the trial; 25 in the usual care group, 33 in the active patch group, and 40 in the placebo patch group.

There were no serious AEs reported by patch users though minor events (skin irritation, headache) were reported by a few subjects. It is not clear whether the events occurred during the active or placebo phase of treatment. Three subjects withdrew due to an adverse event; one after three weeks due to "hyperreaction" and two within the first week due to headache.

Reviewer Comment: There was minimal adverse event information included in this report but the skin irritation and headaches mentioned are not unexpected.

Hanson et al. (2003)[15]
This was a randomized, double-blind, placebo-controlled study of 100 adolescent smokers, age 13 – 19 years comparing nicotine patch and placebo treatment. Approximately half (53%) of the randomized subjects completed the study; 25 subjects randomized to patch and 28 randomized to placebo. Reasons for drop outs during the trial are not provided; however, no subject discontinued the study due to an adverse event.

The most common AE was itching at the site of the patch but there was no significant difference in the placebo versus the active patch except headache which was more common in the placebo group. Subjects were specifically queried about certain adverse events which may have increased the number of reports but most events were mild. There were no serious AEs and no subjects discontinued due to an adverse event. Table 11 summarizes the reported adverse events in this study.

Table 11: Adverse Event Reports (Hanson et al.)

Adverse Event	Patch (n=50), n (%)	Placebo (n=50), n (%)
Any Adverse Event	48 (97.9%)	45 (93.3%)
Headache	27 (56.3%)	34 (75.6%)
Itching at patch site	31 (64.5%)	24 (53.3%)
Sleep problems or abnormal dreams	30 (62.5%)	23 (51.1%)
Joint or muscle aches	28 (58.3%)	23 (51.1%)
Redness at patch site	26 (54.2%)	19 (42.2%)
Lightheadedness/dizziness	20 (41.7%)	22 (48.9%)
Stomachaches	21 (43.8%)	17 (37.8%)

Reviewer Comment: No new or unexpected adverse events were noted.

Killen, et al. (2001)[16]
This study was intended to examine the extent to which adolescents manifest signs and symptoms of nicotine withdrawal and whether treatment with NRT could alleviate the symptoms. Recruited subjects were ages 13 to 18 years, current smokers of at least 10 CPD, and had an expired-air CO level of at least 5 ppm. The protocol required two eight hour sessions. During session 1, subjects had repeated assessment of CO, vital signs, and withdrawal symptoms while following their normal daily activities. At session 2, subjects were not permitted use of any tobacco products and wore either a placebo or 15 mg nicotine patch for the eight hour period. A total of 105 subjects attended session 1; 13 were excluded from the study – 12 for protocol violations and one subject experienced nausea one hour after the patch was applied. There were 92 subjects who completed the study.

There were five adverse event reports in the placebo group and 16 reports in the active patch group. The only significantly different AE was observed for itching (p=0.01). None of the AEs was felt to be severe by the investigator. The nausea that required one participant to discontinue use of the patch was "not clearly attributable to nicotine replacement."

Reviewer Comment: There was an increase in itching reported in users of the nicotine patch. This is not unexpected.

Killen, et al. (2004)[17]
This randomized, double-blind study compared treatment with nicotine patch versus nicotine patch plus bupropion in adolescent smokers, ages 15 to 18 years. A total of 211 subjects were randomized to treatment with the nicotine patch (dose based on CPD) plus either placebo or bupropion SR 150 mg daily. Subjects were treated with placebo or bupropion for one week before the quit date and then with the patch and the oral medication for an additional eight weeks. They were followed for 26 weeks. All subjects received group counseling. About 29% of participants reported using the patches for at least five treatment weeks but 41% reported using the patches for two treatment weeks or less.

A total of 47 complaints were rated as 'severe' by participants; 25 in the patch plus placebo group and 22 in the patch plus bupropion group. The adverse events are shown in Table 12. None of the AEs were judged by the investigator as severe.

Table 12: Reported Adverse Events; Killen et al. (2004)

	Severe		Moderate	
Adverse event	NP + B (n = 103)	NP (n = 108)	NP + B (n = 103)	NP (n = 108)
Dimness of vision	1	1	0	0
Skin rash	1	0	3	4
Nausea	3	4	4	6
Confusion	1	0	0	1
Digestive problems	1	0	1	0
Agitation	0	0	1	1
Headache	1	0	2	1
Weakness	0	2	0	2
Sweating	0	1	0	0
Dizziness	2	1	1	3
Other	12	16	12	17

Note. NP = nicotine patch treatment; B = bupropion.

Reviewer Comment: All subjects in this study were exposed to the nicotine patch. No significant new or unexpected findings were noted.

Rubenstein et al. (2008)[18]
This was a randomized, open-label, trial of weekly counseling alone (control) for eight weeks versus counseling plus six weeks of nicotine nasal spray. Subjects were followed for 12 weeks. Investigators recruited forty adolescent smokers, between 15 and 18 years of age, who smoked ≥ 5 cigarettes daily. Fifty-seven percent of the participants stopped using the nasal spray after one week of treatment. The most commonly reported AE was nasal irritation and burning (34.8%) followed by complaints about the taste and smell (13%).

Reviewer Comment: This small study only exposed subjects to the nicotine nasal spray. Nasal burning – the most commonly reported adverse event – is not likely to be a problem with use of the nicotine polacrilex lozenge. Data from this study does not significantly contribute to this NDA review.

Hanson et al. (2008)[19]
This randomized, open-label observational trial examined whether adolescents age 13 -19 years who were not interested in quitting could reduce cigarette smoking. Subjects were treated for six

weeks. The first two weeks were baseline visits; then participants were randomized to placebo (n=36), nicotine patch (n=34), or nicotine gum (n=33) and treated for an additional four weeks. Subjects were followed for six months. Of participants, 91.3% (n=94/103) completed the six weeks treatment period, 85.1% completed the 3-month follow-up visit and 71.3% completed the 6-month follow-up visit. The published report did not include any information regarding adverse events.

Reviewer Comment: No information regarding adverse events is included in this publication. The study had a low attrition rate (compared to the other studies) which could indicate the medications were reasonable well tolerated. Subjects continued to smoke cigarettes, however, which may also have contributed to the higher subject retention. Data from this study does not significantly contribute to this NDA review.

Hurt et al. (2000)[20]
This was a nonrandomized, open-label trial of 101 adolescents, aged 13-17 years and smoking at least 10 CPD treated with a 15 mg/16 hour nicotine patch. Subjects were treated for six weeks with follow-up visits at 12 weeks and 6 months. A total of 71 participants completed the entire six weeks of treatment.

Five subjects discontinued the study due to an adverse event. (No additional details were included in the publication.) The most commonly reported adverse events were upper respiratory infection (n=44), headache (n=43), nausea and/or vomiting (n=13), skin reaction at the patch site (n=12), and sleep disturbance (n=10). The authors report there was no difference in the frequency of adverse events in the subjects who completed the patch therapy compared to those who did not.

Reviewer Comment: This report provides minimal information regarding adverse events. There does not appear to be an increase in reports for those that used the patch for the full six weeks of treatment, but since there was no control group, the data is of limited value.

Smith et al. (1996)[21]
This was a nonrandomized, open-label trial of 22 adolescent smokers, aged 13-17 years and smoking at least 20 CPD. Subjects were treated with nicotine patch therapy for eight weeks (22 mg/day for 6 weeks and 11 mg/day for 2 weeks). Subjects also received weekly behavioral counseling for eight weeks with follow-up visits at 3 and 6 months. Of the 22 participants, 19 (86%) completed patch therapy. The three subjects that dropped out before completion represented noncompliance issues and did not drop out due to an adverse event.

Eighteen of the 22 subjects experienced at least one adverse event and 15 subjects reported some type of skin reaction: 12 reported erythema only, one had erythema and edema, and two had erythema and vesicles. Other reported adverse events were headache (41%), nausea and vomiting (41%), tiredness (41%), dizziness (27%), and arm pain (23%). None of these events were considered serious.

Reviewer Comment: This small, uncontrolled study does not add much useful information though the subjects did appear to tolerate the patch and no new safety signals were identified.

8 Postmarket Experience

The GSK worldwide clinical safety database was searched on 26 October 2011 using the following criteria:

- **Data lock point(s):** 31 October 2007 to 30 October 2010
- **Report types:** All spontaneous reports, post-marketing surveillance reports, and unblinded serious clinical trial reports (attributable and non-attributable).
- **Suspect drug:** nicotine patch and nicotine polacrilex (gum and lozenge)
- **Age:** less than 18 Years (Exposure to nicotine via breast milk and in-utero exposure reports have been excluded.)

A total of 68 reports were retrieved. Two of the reports documented the use of nicotine patch and gum or lozenge; these two reports are presented in both the nicotine patch and oral formulations groups. One report did not specify the oral formulation. GSK included this report within the gum group. Table 13 shows a breakdown of the reports.

Table 13: Breakdown of GSK Worldwide Reports for Consumers < 18 years old

Reports	Nicotine patch	Oral formulations of nicotine	
		Gum	Lozenge
Serious[1] and non-serious	40	16	14
Serious	3	4	2
Healthcare professional as report source	3	1	2
Healthcare professional as report source and serious	0	0	0
US reports	16	9	6

[1] Serious report: a report where at least one of the adverse events is serious.

Age and Gender distribution

Nicotine Patch (n=40)

- The gender was specified in 38 reports; 20 females and 18 males.
- In 37 reports the exact age was specified. The range was 21 months to 17 years. In two reports, the age was listed as ‘child’ and in one report as ‘teenager.’

Nicotine Gum (n=16)

- The gender was specified in 13 reports; 4 females and 9 males.
- In 12 reports the exact age was specified. The range was 3 to 17 years. In two reports, the age was listed as 'child,' in one report as 'teenager,' and in one report as '14-15 years.'

Nicotine Lozenge (n=14)

- The gender was specified in all reports; 6 females and 8 males.
- The age was specified in all reports. The range was 1 to 17 years.

Evaluation of Patient Sub-Populations

The sponsor performed a sub-group analysis by age – children (<12 years) and adolescents (12 – 17 years). The summary of AE reports by formulation and age is shown in Table 14.

Table 14: Summary of Adverse Event reports by Age and Nicotine Formulation

Reports	Nicotine Patch		Nicotine Gum		Nicotine Lozenge	
	Serious	Total	Serious	Total	Serious	Total
Children	0	4	2	5	1	8
Adolescent	3	36	2	11	1	6

Children (<12 years)

There were four reports for the nicotine patch; two were accidentally exposed. Of the other two, one developed a tremor and diplopia and the other patient's arm was swollen at the application site. There were five reports for the nicotine gum. Two of these were serious reports from consumers after the children ingested "several pieces" of gum and developed nicotine poisoning. Both recovered after hospitalization. Two other patients also accidentally ingested the gum; one vomited and one experienced asthenia, dizziness, and vomiting. Both of these patients also recovered. The final report was a possible overdose in a 3-year-old who chewed a piece of 4 mg gum with no reported adverse event. There were eight reports for the nicotine lozenge; six reports of accidental exposure, one report of maladministration, and one report of intentional misuse. Only two of the lozenge reports had associated adverse events: one 3-year-old experienced vomiting and was hospitalized overnight and the other patient experienced vomiting and salivary hypersecretion. The single report of intentional misuse involved a 4-year-old who took two 4 mg lozenges but it is not clear he consumed them.

Adolescents (12 to 17 years)

There were 36 AE reports for the *nicotine patch*; three were serious.

- 15-year-old with asthma who was also using the nicotine lozenge; she experienced application site reaction and shortness of breath. The lozenge was discontinued and the outcome is unknown.

- 16-year-old who was also taking salbutamol and beclomethasone; he developed dizziness, headache, vomiting, and difficulty standing the same day he began using the nicotine 25 mg patch. The nicotine was discontinued and the events resolved.
- 16-year-old who developed severe application site reactions including blistering, irritation, burning, and extreme heat after using a 25 mg nicotine patch for an unspecified period. The dose was reduced and the events improved.

There were 33 non-serious reports for the nicotine patch in this age group. Most (n=12) involved application site reactions. Other common reports were intentional drug misuse (n=5), drug administration error (n=3), and medication error/accidental exposure (n=3). There were five reports that listed events known to be related to the patch (nausea, vomiting, headache, dizziness, and abdominal pain). It was noted that all three cases of drug administration error occurred in 17-year-olds who were using the nicotine patch in an effort to quit smoking.

There were 11 AE reports for the *nicotine gum*; two were serious and both cases involved an overdose of the gum.

- One patient took 30-45 pieces of gum within an hour, developed dizziness and stomach ache, and then collapsed and was in a coma.
- The second patient ingested up to 45 pieces of gum and was hospitalized with dizziness. The outcome of both patients is unknown.

Other non-serious reports included mal administration (n=2), accidental exposure (n=1), and intentional drug misuse (n=1). Four patients reported adverse events known to occur with nicotine oral formulations (tachycardia, tremor, throat irritation, malaise, vomiting, and nausea).

There were six AE reports for the *nicotine lozenge*; only one was serious. This is the same report described above (the 15-year-old using both the patch and lozenge). Three reports included adverse events listed for oral nicotine formulations (throat irritation/pain and vomiting). Two other reports described decrease appetite and chest pain. The chest pain resolved after the lozenge was discontinued.

Summary of Reported Adverse Events

Nicotine Patch (n=40)

There were 111 adverse events (AEs) included in the 40 reports for the nicotine patch. Most events were in the MedDRA System Organ Class (SOC) of General disorders and administrative site conditions (primarily application site events such as pruritis and erythema), Gastrointestinal disorders (predominately nausea), Nervous system disorder (headache and dizziness), Psychiatric disorders (mostly intentional drug misuse), and Injury, poisoning and procedural complications (primarily drug administration/medication errors). Table 15 summarizes the SOCs and preferred terms with the most reported AEs.

Table 15: Summary of Most Common Events by SOC for Nicotine Patch Reports

SOC	Preferred Term	Number of Events	SOC Event Total	SOC Case Total
Gastrointestinal disorders	Abdominal discomfort	1	15	12
	Abdominal pain upper	2		
	Nausea	8		
	Salivary hypersecretion	1		
	Vomiting	3		
General disorders and administrative site conditions	Adverse event	1	43	24
	Application site burn	2		
	Application site erythema	7		
	Application site irritation	1		
	Application site pain	2		
	Application site papules	1		
	Application site pruritis	9		
	Application site rash	4		
	Application site reaction	3		
	Application site scab	1		
	Application site scar	1		
	Application site swelling	2		
	Fatigue	2		
	Feeling Abnormal	1		
	Hunger	1		
	Malaise	3		
	No adverse event	1		
Injury, poisoning and procedural complications	Accidental drug intake by child	1	12	12
	Accidental exposure	1		
	Drug administration error	6		
	Medication error	2		
	Thermal burn	2		
Nervous system disorders	Dizziness	5	14	10
	Dysstasia	1		
	Headache	6		
	Sensory disturbance	1		
	Tremor	1		
Psychiatric disorders	Abnormal dreams	2	12	8
	Depressed mood	1		
	Fear	1		
	Intentional drug misuse	6		
	Obsessive thoughts	1		
	Sleep disorder	1		

Nicotine Gum (n=16)

There were 44 total events in the 16 AE reports for the nicotine gum. Most events were in the Injury, poisoning and procedural complications SOC and were related to accidental drug administration or exposure. The common events, listed by preferred term and SOC, are shown in Table 16.

Table 16: Summary of Most Common Events by SOC for Nicotine Gum Reports

SOC	Preferred Term	Number of Events	SOC Event Total	SOC Case Total
Gastrointestinal disorders	Abdominal pain upper	1	8	7
	Lip disorder	1		
	Nausea	3		
	Vomiting	3		
	No adverse event	1		
Injury, poisoning and procedural complications	Accidental exposure	3	14	11
	Drug administration error	2		
	Fall	1		
	Overdose	3		
	Thermal burn	1		
	Tobacco poisoning	2		
	Wrong drug administered	2		
Nervous system disorders	Coma	1	6	4
	Dizziness	3		
	Loss of consciousness	1		
	Tremor	1		

Nicotine Lozenge (n=14)

There were 34 total events in the 14 AE reports for the nicotine lozenge. Most of the events were in the Injury, poisoning and procedural complications SOC and were related to accidental drug administration or exposure. The common events, listed by preferred term and SOC, are shown in Table 17.

Table 17: Summary of Most Common Events by SOC for Nicotine Lozenge Reports

SOC	Preferred Term	Number of Events	SOC Event Total	SOC Case Total
Gastrointestinal disorders	Retching	1	5	3
	Salivary hypersecretion	1		
	Vomiting	3		
General disorders and administrative site conditions	Application site burn	1	6	3
	Application site pruritis	1		
	Application site reaction	1		
	Chest pain	1		
	Drug ineffective	1		
	No adverse event	1		
Injury, poisoning and procedural complications	Accidental drug intake by child	1	11	11
	Accidental exposure	5		
	Drug administration error	4		
	Thermal burn	1		

Overall Summary

Most of the reports of adverse events in children (< 12 years of age) were due to accidental exposure to single doses of nicotine. In several cases (n=7), there were no associated symptoms related to the nicotine exposure and the majority of the reported events were gastrointestinal complaints (nausea and vomiting) or neurological events (tremor or dizziness). Most of the

adverse event reports in adolescents (12 to 17 years of age) were non-serious and many included events known to be associated with nicotine products.

The sponsor concludes "NRT has been shown to be well tolerated in adolescent populations and has a similar PK profile to that of adults." The review of the worldwide pharmacovigilance data does not raise any new safety issues.

Reviewer Comment: The GSK worldwide pharmacovigilance database has a small number of reports of adverse events in those < 18 years of age. When the population is narrowed to those reports related to the nicotine lozenge, the number becomes quite small. The pattern of reports, however, is not concerning. Most of the events were not serious and were known possible reactions to the nicotine products. I agree that this data did not raise any new safety issues.

9 Appendices

9.1 Literature Review/References

Six publications (references 11-15) summarizing five randomized, double-blind, placebo-controlled studies assessing the efficacy of NRT for smoking cessation in adolescents were included in this application. The studies are summarized in sections 5.3.2 – 5.3.6 and 7.1.1. Six additional publications of studies (references 16-21) with adolescent subjects are reviewed for safety in section 7.1.1.

9.2 Labeling Recommendations

The Drug Facts labeling proposed by GSK on April 15, 2011 is shown in Figure 1. The only proposed change from current labeling is highlighted in yellow and includes the following statement under ***Directions***:

"If you are under 18 years of age, ask a doctor before use. (b) (4) (b) (4)"

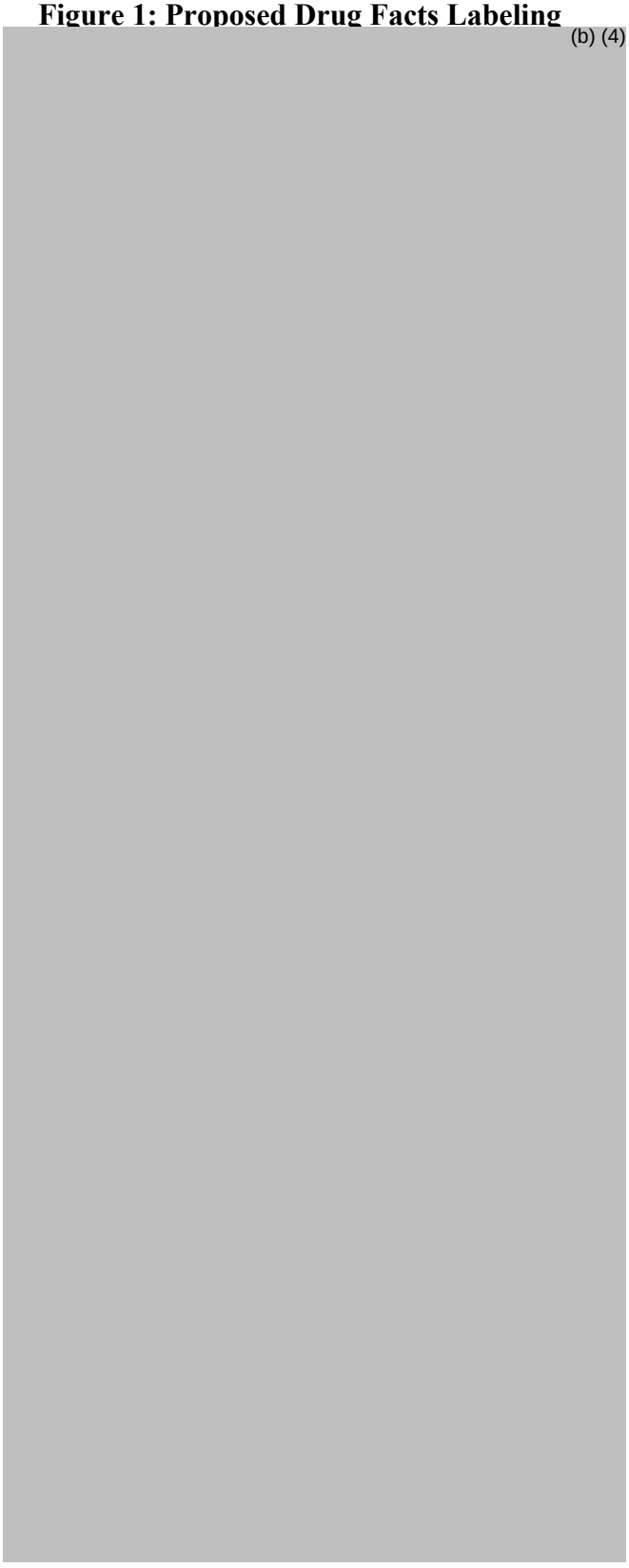
The specific wording of this statement has not been fully negotiated with the sponsor and the other FDA reviewers. At this time, the recommendation is for the statement to be revised to:

"If you are under 18 years of age, ask a doctor before use; (b) (4) (b) (4)."

Final recommendations for product labeling will be made by the entire review team.

Figure 1: Proposed Drug Facts Labeling

(b) (4)



[1] Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. JAMA 2004; 291:1238-45.
[2] Results from the 2006 National Survey on Drug Use and Health: national findings 2006. (Accessed at **www.samhsa.gov/nhsda htm <http://www.samhsa.gov/nhsda.htm>.**)
[3] Drug Research and Children. (Accessed at http://www fda.gov/Drugs/ResourcesForYou/Consumers/ucm143565.htm.)
[4] Regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients; Final Rule. December 2, 1998. (Accessed at http://www.fda.gov/ohrms/dockets/98fr/120298c.txt.)
[5] Complaint, Association of American Physicians and Surgeons, Inc., et al., v. United States Food and Drug Administration, Civil Action No. 1:00CV02898 (HHK) (D.D.C. December 4, 2000). (Accessed at http://www fda.gov/ohrms/dockets/dailys/02/Jul02/070802/02n-0152_c000062_02_tab_01_vol2.pdf.)
[6] Federal court invalidates the FDA Pediatric rule: *AAPS v. FDA*. (Accessed at http://www.law.uh.edu/healthlaw/perspectives/Children/021223Federal.html.)
[7] Approval Letter, NDA 21-330, dated October 31, 2002. (Accessed at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2002/21330ltr.pdf.)
[8] Postmarketing Commitment Letter to GSK, dated August 19, 2008.
[9] Meeting minutes for meeting held between FDA and GSK on February 4, 2009, dated March 5, 2009.
[10] Office of Clinical Pharmacology and Biopharmaceutics NDA review, NDA 21-330, Dr. Shinja Kim and Dr. Suresh Doddapaneni, dated July 26, 2001.
[11] Roddy E, Romilly N, Challenger A, Lewis S, Britton J. Use of nicotine replacement therapy in socioeconomically deprived young smokers: a community based pilot randomized controlled trial. *Tob Control,* 5/2006, (15) 373-376.
[12] Moolchan ET, Robinson ML, Ernst M, Cadt JL, Pickworth WB, Heishman SJ. Safety and Efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. *Pediatrics,* 4/2005, (115) 407-414.
[13] Wold AL, Whitmore EA, Gianani EJ, Mikulich-Gilbertson SK. Nicotine Patch Therapy for Adolescent Smokers: A Pilot Study. 2005, Presented at: College on Problems of Drug Dependence Conference.
[14] Stotts RC, Roberson PK, Hanna EY, Jones SK, Smith CK. A randomized clinical trial of nicotine patches for treatment of spit tobacco addiction among adolescents. *Tobacco Control*, Suppl 4, 2003, (12) IV11-IV15.
[15] Hanson K, Allen S, Jensen S, Hatsukami D. Treatment of adolescent smokers with the nicotine patch, *Nicotine Tob Res*, 4/2003, (5) 515-526.
[16] Killen JD, Ammerman S, Rojas N, et al. Do Adolescent Smokers Experience Withdrawal Effects when Deprived of Nicotine. *Experimental and Clinical Psychopharmacology*, 2001 (9) 2: 176-182.
[17] Killen JD, Robinson TN, Ammerman S, et al. Randomized Clinical Trial of the Efficacy of Bupropion Combined with Nicotine Patch in the Treatment of Adolescent Smokers. *Journal of Consulting and Clinical Psychology,* 2004 (72) 4: 729-735.
[18] Rubinstein ML, Benowitz NL, Auerback GM, and Moscicki A. A Randomized Trial of Nicotine Nasal Spray in Adolescent Smokers. *Pediatrics*, 2008 (122) 3: e595-e600.
[19] Hanson K, Zylla E, Allen S, Li A, and Hatsukami DK. Cigarette reduction: An intervention for adolescent smokers. *Drug and Alcohol Dependence*, 2008 (95); 164-168.
[20] Hurt RD, Croghan GA, Beede SD, et al. Nicotine Patch Therapy in 101 Adolescent Smokers. *Archives of Pediatric and Adolescent Medicine*, 2000 (154): 31-37.
[21] Smith TA, House RF, Croghan IT, et al. Nicotine Patch Therapy in Adolescent Smokers. *Pediatrics*, 1996 (98): 659-667.

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/s/

PRISCILLA C LYON
04/11/2012

DAIVA SHETTY
04/11/2012

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 21330 **Applicant: GlaxoKline** **Stamp Date: 08/09/11**

Drug Name: Nicorette Lozenge **NDA/BLA Type: NDA**

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				**Electronic**
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	**X**			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	**X**			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	**X**			
5.	Are all documents submitted in English, or are English translations provided when necessary?	**X**			
6.	Is the clinical section legible so that substantive review can begin?	**X**			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional and Center policies?			**X**	
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?			**X**	
9.	Has the applicant submitted the integrated summary of safety (ISS)?			**X**	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			**X**	
11.	Has the applicant submitted a benefit-risk analysis for the product?			**X**	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			**X**	**PREA - Efficacy supplement**
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			**X**	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:				

File name: 4_Clinical Filing Checklist for a New NDA_BLA110207

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			**X**	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			**X**	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			**X**	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			**X**	
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			**X**	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			**X**	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			**X**	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			**X**	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			**X**	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			**X**	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			**X**	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	**X**			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			**X**	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			**X**	**PREA Efficacy Supplement Under Review**
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			**X**	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			**X**	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			**X**	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			**X**	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			**X**	
34.	Are all datasets to support the critical safety analyses available and complete?			**X**	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			**X**	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			**X**	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			**X**	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			**X**	
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			**X**	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Jacqueline A. Spaulding	Sept. 8, 2011
Reviewing Medical Officer	Date
Clinical Team Leader	Date

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/s/

JACQUELINE A SPAULDING
09/27/2011

CELIA J WINCHELL
09/27/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 21-330 **Applicant: GlaxoSmithKline** **Stamp Date: 8/9/2011**

Drug Name: Nicorette Lozenge **NDA/BLA Type: NDA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				This is an electronic submission.
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?		X		Labeling reviewers from the Division of Nonprescription Regulation (DNRD) will request draft label in electronic format.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?		X		The applicant has been requested to provide
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?		X		
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(2); the application relies extensively on published literature
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			X	Efficacy review is undertaken by the Division of Anesthesia

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 Indication: Pivotal Study #2 Indication:				and Analgesia Products (DAAP)
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?				
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	No new clinical studies are included in this application.
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	GSK does not propose to expand the target population to adolescents.

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	No new clinical studies are included in this application.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			It was agreed at the February 4, 2009 meeting, GSK can submit full published literature reports to support fulfillment of PREA requirement.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	GSK does not propose to expand the target population to adolescents.
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	This supplement aims to address the requirement data in children aged 10 to 17, which was deferred from the 2002 NDA approval.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	No new studies are included in this application.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

Reviewer comment:
This supplemental application contains no new clinical data. The only study sponsored by the applicant was study S1330074, a pharmacokinetic study assessing three nicotine replacement therapy formulations in 45 adolescents aged 13 to 17 years. This study was previously reviewed by DNCE and the Pediatric Maternal Health Staff; the reviews concluded that findings from S1330074 were inadequate to satisfy PREA requirements. The submission of this efficacy supplement is GSK's response to this determination.

GSK does not propose to expand the target population for Nicorette lozenge to include adolescents under the age of 18 years. The applicant has proposed to include the following statement into product labeling: "If you are under 18 years of age, ask a doctor before use. (b) (4) ."

Safety data provided in this application include:

- 45 publications
  - 6 trials (7 publications, 1 in abstract form) are randomized, double-blind, placebo-controlled trials in adolescent smokers, including 776 total subjects; no studies assessed lozenge formulation.
  - 1 randomized, double-blind, active-controlled trial in adolescent smokers, including 211 total subjects. Products assessed were nicotine patches & bupropion.
  - 2 randomized, open-label, controlled trials, including 143 total subjects. Neither study assessed the lozenge.
  - 2 uncontrolled trials, 123 total subjects. Neither study assessed the lozenge.
- Postmarketing periodic adverse event reports from October 31, 2007 to October 30, 2010
- Study S1330074, a dose-escalating, pharmacokinetic evaluation of nicotine patch, gum, and lozenge formulations in 45 children 13 to 17 years of age

The clinical summary provided by the applicant presents an integrated assessment of efficacy; the summary did not provide an integrated overview of safety.

From the perspective of clinical safety, the following information request will be conveyed to the applicant:

1. Provided an Integrated Summary of Safety on NRT use in adolescents, which should include:
   - An analysis of all adverse events reported to the postmarketing safety database concerning individuals under the age of 18, these events should be summarized using MedDRA coding. Time frame for the summary can be limited to October 31, 2007 to October 30, 2010 to correspond to the last three periodic safety reports.
   - A summary of safety data from clinical studies (including the literature cited and S1330074).
2. Per 21 CFR 54 and 21 CFR 314.50, you are required to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. Please

clarify whether you have provided this information for investigators involved in study S1330074. Please clarify whether you have provided this information for investigators involved in study S1330074.

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/s/

CHRISTINA Y CHANG
09/19/2011

DAIVA SHETTY
09/20/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21330/S-013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 21-330	Submission Date: 7/29/11
Submission Type; Code:	Efficacy Supplement 013 Postmarketing Requirement: Pediatric Research Equity Act
Brand/Code Name:	Nicorette® lozenge
Generic Name:	Nicotine polacrilex
Primary Reviewer:	David Lee, Ph.D.
Team Leader:	Yun Xu, Ph.D.
OCP Division:	DCP 2
OND Division:	Division of Anesthesia, Analgesia, and Addition Products
Sponsor:	GlaxoSmithKline
Formulation; Strength(s):	Lozenge; 2 and 4 mg
Proposed Indication:	Reduction of withdrawal symptoms, including Nicotine Craving associated with quitting smoking.
Proposed Dosage Regimen:	• Weeks 1-6: 1 piece every 1 – 2 h; • Weeks 7–9: 1 piece every 2 – 4h; • Weeks 10-12: 1 piece every 4-8 h

Introduction

GlaxoSmithKline (GSK) has submitted a Supplement 013 to New Drug Application 21330, Nicorette® Lozenges (nicotine polacrilex). This is to fulfill the requirements associated with the Pediatric Research Equity Act (PREA) as post marketing requirement (PMR) for Nicorette Lozenge (Sequence 018, 2/19/10). Reference was made to the Agency's response (7/15/11) which the Agency's noted that "We have reviewed your submission and conclude that the terms of the requirement were not met for the following reason: Data to support the fulfillment of your post marketing requirement (PMR) was not submitted as an efficacy supplement." On 2/4/09 the Applicant met with the Agency to discuss comments provided by the Agency (letter dated 8/19/08) regarding the requirements associated with the PREA and lozenges for nicotine replacement therapy (NRT); during the meeting the Applicant was asked to 1) submit an analysis of the existing published literature to demonstrate lack of efficacy of nicotine replacement therapy in adolescents; and, 2) provide pharmacokinetic data to establish the efficacy bridge from nicotine patch and gum formulations to nicotine polacrilex lozenge. It is noted, from an administrative perspective, that the submission date for this Supplement was 3/25/11; however, the Applicant did not submit a user fee with the submission. On 5/19/11 the Applicant was informed that a user fee is required, and, upon the receipt of the user fee, the review clock started on 7/29/11.

In this submission, the Applicant submitted a comprehensive review of the published literature, including full text articles and primary data where available, as well as a brief

summary of the GSK adolescent PK study, Protocol S1330074, entitled "A Pharmacokinetic and Safety Study of (b) (4) Nicotine Replacement Therapy Formulations in Adolescent Smokers." It is noted that Study S1330074 was submitted to N 21330 in 8/20/07. From a clinical pharmacology perspective, Study report S1330074 was reviewed.

Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in the current application. From clinical pharmacology perspective, the submitted information in this supplement is acceptable.

Due to the recruitment difficulties, no 10 – 12 year olds subjects participated in Study S1330074. The nicotine pharmacokinetic data submitted in pediatric patients 13-17 years are acceptable (Study S1330074). Comparing the historical adult nicotine pharmacokinetic parameters and the pediatric (13-17 years old) nicotine pharmacokinetic parameters presented in this submission, the nicotine pharmacokinetic parameters were comparable.

Background

NDA 21-330, Commit® nicotine lozenges, nicotine polacrilex 2 mg and 4 mg lozenges, was approved by the Division of Nonprescription Clinical Evaluation (HFD-560) on October 31, 2002. Among the conditions for approval was that the Applicant conducts a pediatric study for patients 10-17 years, and submit to FDA by October 31, 2007. As part of that condition, the Agency waived the requirements for patients under age 10.

The Applicant stated that they have met that condition and provided a final study report for Study S1330074, "*A Pharmacokinetic and Safety Study of Nicotine Replacement Therapy Formulations in Adolescent Smokers*". This study characterized the pharmacokinetic profiles of three nicotine replacement therapy (NRT) formulations *Commit lozenge, Nicoderm CQ patch* and *Nicorette gum* in adolescent smokers.

Discussion on Study S1220074

Reviewer's overall comments

1. This study was originally designed to characterize the pharmacokinetics in adolescents (10 to 17 years old) (b) (4)

2. No pediatric patients between 10 - 12 years were studied due to recruitment difficulties.

3. This study was a single dose, open label, dose escalation study:

Cohort	Treatment	Dosage	
		Session One	Session Two
1	Nicotine Lozenge	2 mg	4 mg
2	Nicotine Transdermal Patch	14 mg	21 mg
3	Nicotine Gum	2 mg	4 mg

4. Washout period between sessions were 12 hours. Subjects were permitted to smoke between sessions except for the 12-hour period before (baseline) and the 12-hour blood collection period after dosing at each session. Subjects were domiciled for approximately 24 hours during each session. Thus, some of the treatment arms showed nicotine levels at baseline at the start of the second session. For those with measurable nicotine baseline, PK parameters were obtained with a baseline adjusted analysis. Thus, the data presented in the study report is acceptable.

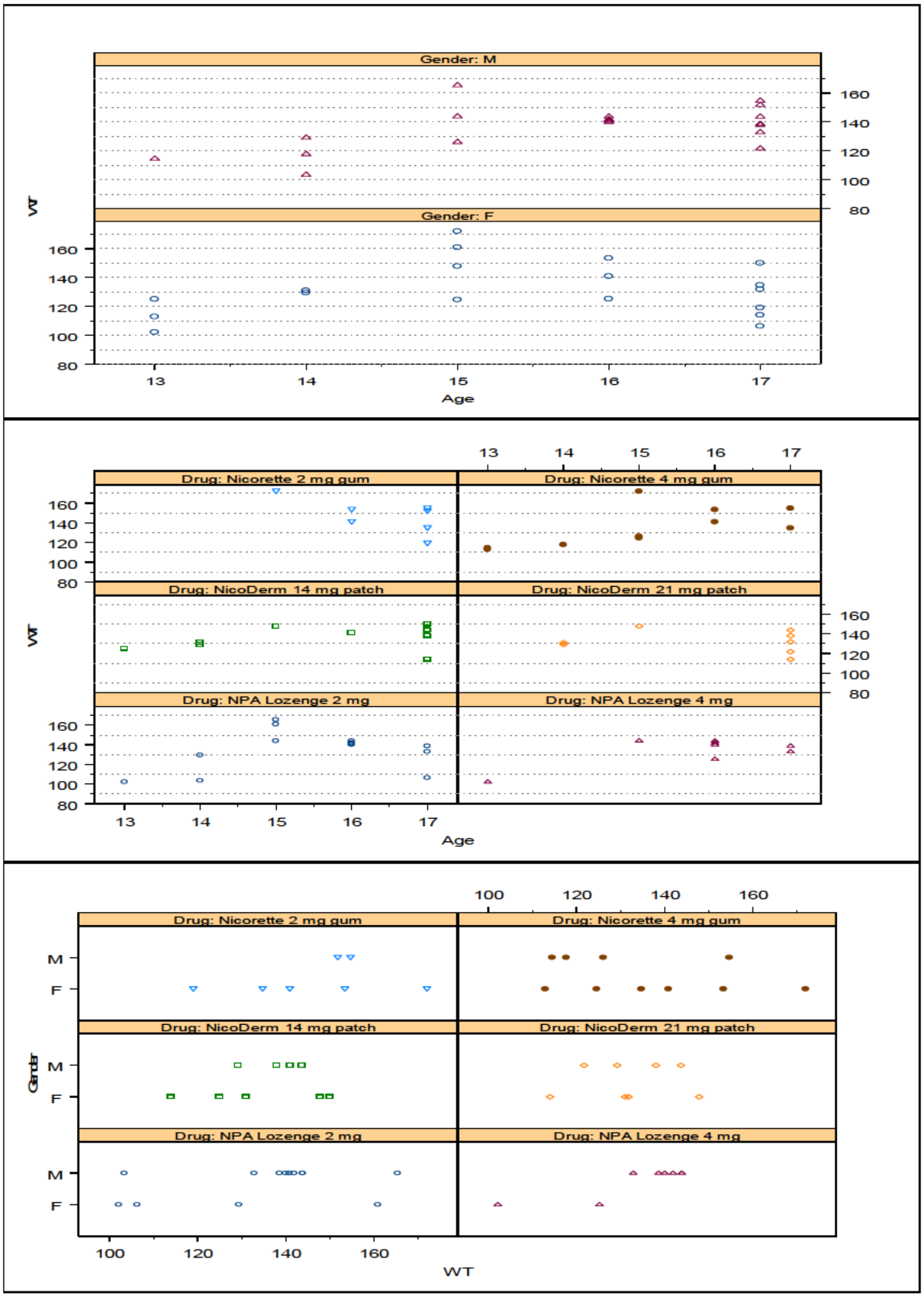
5. There were 8 subjects enrolled into the study twice. Five and 3 subjects were in lozenge/patch and patch/gum cohorts, respectively.

Lozenge Cohort	Patch Cohort	Gum Cohort
Subject Number		
4	26	
5	27	
9	28	
11	29	
13	29	
	31	51
	34	53
	38	65

From PK analysis perspective, with adequate washout period between dosing, the PK parameters derived from these subjects will have no critical impact on the overall findings. Thus, the data presented in the study report is acceptable.

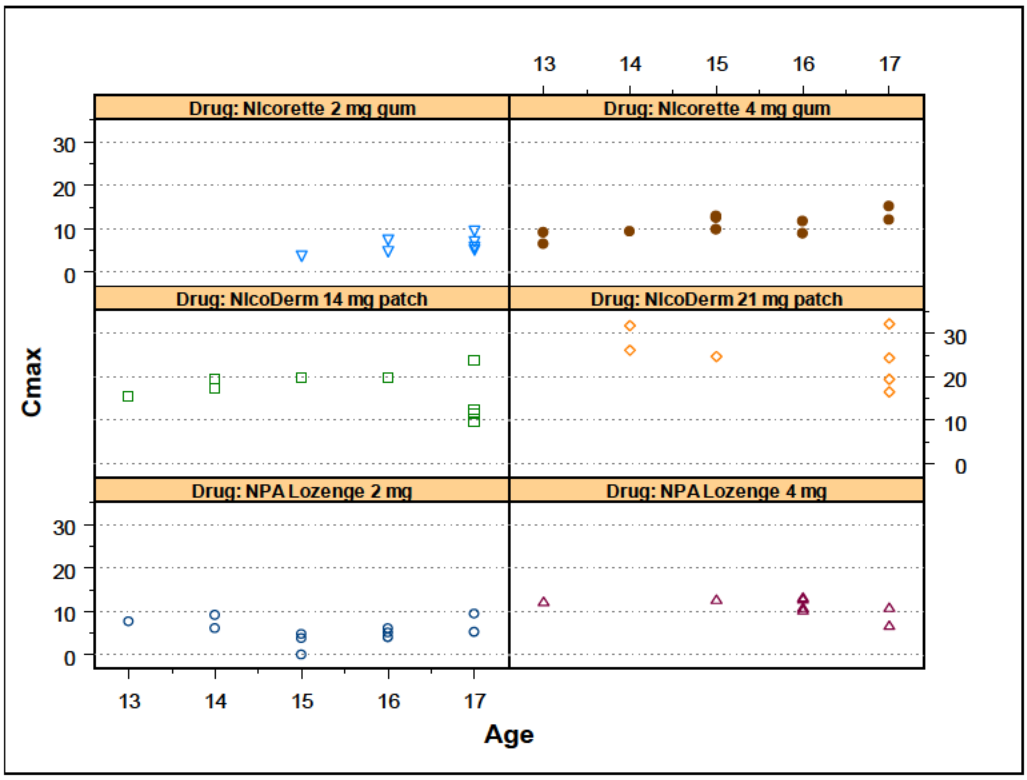
6. Demographic distribution

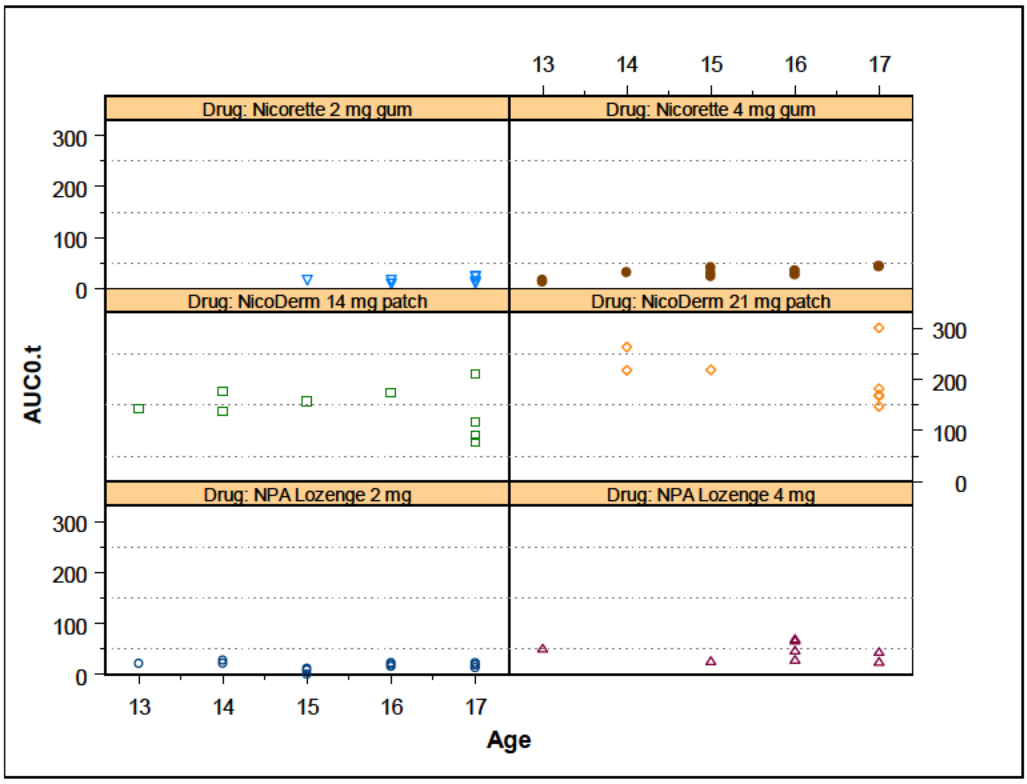
There were no trends of younger children weighing less than the older children. There were also no trends of female subjects weighing less than the male subjects. The number of male and female subjects was somewhat evenly spread out between treatment groups.


Gender: M
Gender: F
WT
Age
Drug: Nicorette 2 mg gum
Drug: Nicorette 4 mg gum
Drug: NicoDerm 14 mg patch
Drug: NicoDerm 21 mg patch
Drug: NPA Lozenge 2 mg
Drug: NPA Lozenge 4 mg
Gender
M
F
WT

7. Cmax and AUC values and age

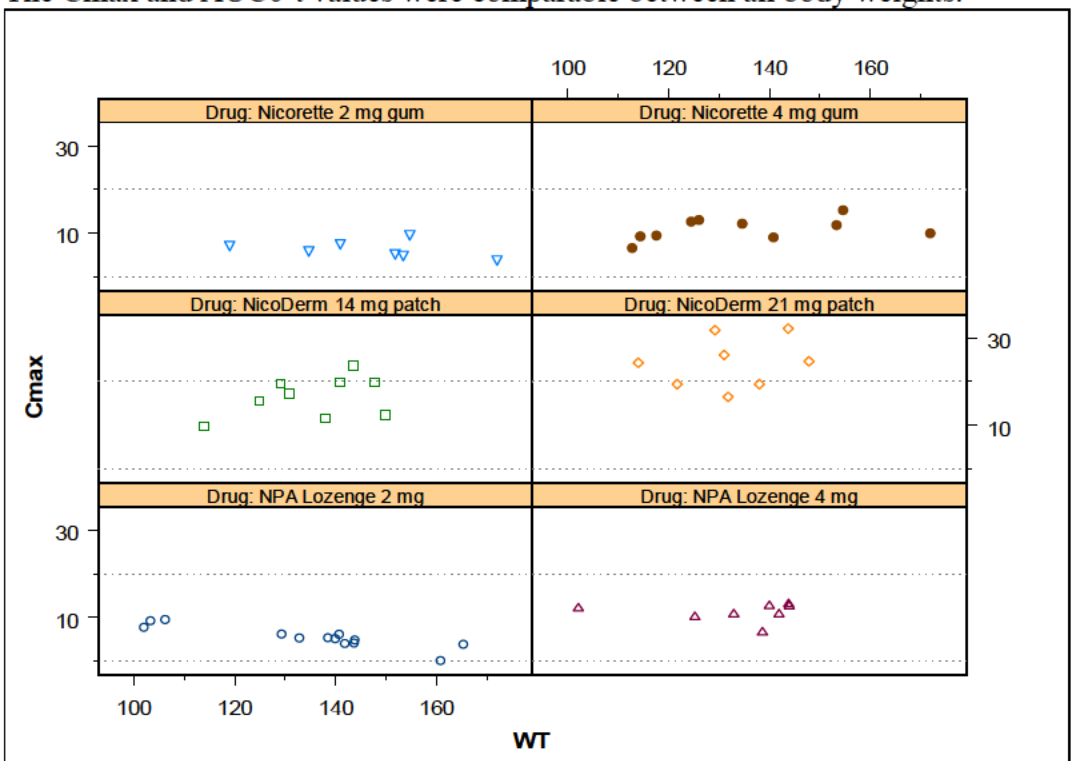
The Cmax and AUC0-t values were comparable between younger and older age groups.

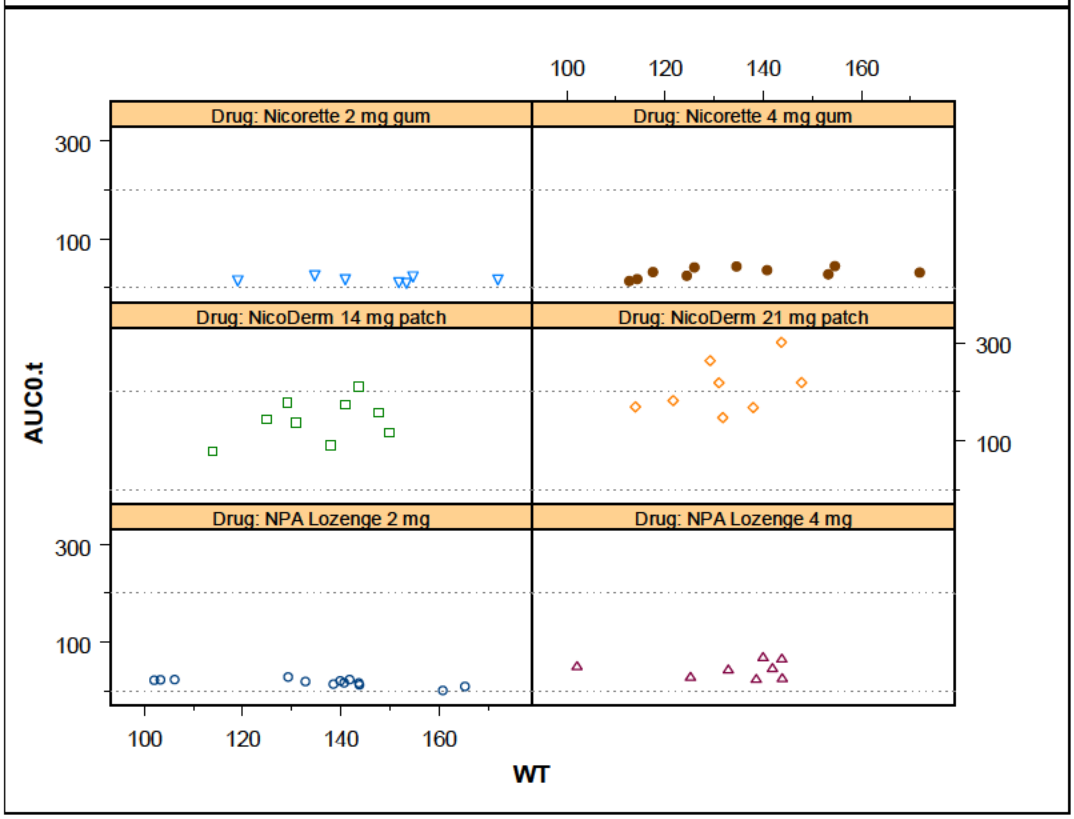




8. Cmax and AUC values and weight

The Cmax and AUC0-t values were comparable between all body weights.





9. Pediatric values compared to adults values

For comparison purposes, the adult nicotine PK information was extracted from the various NDA reviews:

	Dose	Cmax	AUC0-inf
Nicotine Gum[#]	2 mg	4.0 ± 1.5	11.3 ± 7.6
	4 mg	10.0 ± 2.9	34.6 ± 17.6
Nicoderm CQ[##]	14 mg	–	–
	21 mg	19.17 ± 4.58	317.2 ± 73.17
Commit Lozenge[#]	2 mg	4.4 ± 1.7	14.1 ± 9.2
	4 mg	10.8 ± 4.7	44.0 ± 26.5

#CPB Review Dr. Shinja Kim (signed off 7/19/01) N21-330 original submission (submission date: 12/15/00)
##CPB Review Dr. Yuanchao Zhang (signed off 8/26/04) N20-165 s-021 (submission date: 4/23/04) for 21 mg strength.

The following pediatric PK information currently submitted is compared to the above table:

	Dose	Cmax	AUC0-inf
Nicotine Gum	2 mg	6.2 ± 1.9	19.7 ± 6.0
	4 mg	10.8 ± 2.5	34.9 ± 11.7
Nicoderm CQ	14 mg	16.4 ± 4.6	227.6 ± 67.2
	21 mg	24.3 ± 5.7	327.8 ± 114.5
Commit Lozenge	2 mg	5.4 ± 2.5	21.4 ± 6.1
	4 mg	11.1 ± 2.1	44.5 ± 16.2

The nicotine values in above tables indicate that the systemic exposure of nicotine in adults and 13-17 year old pediatric subjects is generally comparable for the same product at same dose.

Study Design

Study S1330074 was a single-center, single dose, open label and dose escalation study. This study was originally designed to characterize the pharmacokinetics of three nicotine replacement therapy (NRT) formulations, Commit lozenge, Nicoderm CQ patch, (b) (4) and, Nicorette gum in adolescent smokers, 10 – 17 years of age. (b) (4)

At Session 1, the lower dose of assigned formulation was studied: 2 mg lozenge, 14 mg patch, or 2 mg gum. At Session 2, the higher dose of assigned formulation was studied: 4 mg lozenge, 21 mg patch, or 4 mg gum.

Cohort	Treatment	Session 1	Session 2
1	Nicotine Lozenge	2 mg	4 mg
2	Nicotine Transdermal Patch	14 mg	21 mg
3	Nicotine Gum	2 mg	4 mg

Lozenges (2 mg and 4 mg) were moved from side to side of the mouth every four seconds until completely dissolved. Patches (14 mg and 21 mg) were applied to skin for 12 hours. Gum (2 mg and 4 mg) was chewed once every four seconds, alternating the gum between both sides of the mouth every 30 seconds for a total of 30 minutes.

No pediatric patients between 10 - 12 years of age were studied, rather than planned 10 – 17 years of age. All subjects received nine blood draws over 12 hours relative to the dosing of the formulation for Sessions 1 and 2. There was a wash-out period of 12 hours between Sessions 1 and 2.

Results

1. Due to the recruitment difficulties, no 10 – 12 year olds subjects participated in the study. The following table shows the breakdown of the age groups screened at the beginning of the study.

Overall:

Age	Total N	Male subjects	Female subjects
13	5	1	4
14	6	3	3
15	7	2	5
16	11	6	5
17	17	10	7

Bias – More 16 and 17 year olds recruited

Treatment Group A

Age	Total N	Male subjects	Female subjects
13	1	0	1
14	2	1	1
15	3	1	2
16	5	4	1
17	5	3	2

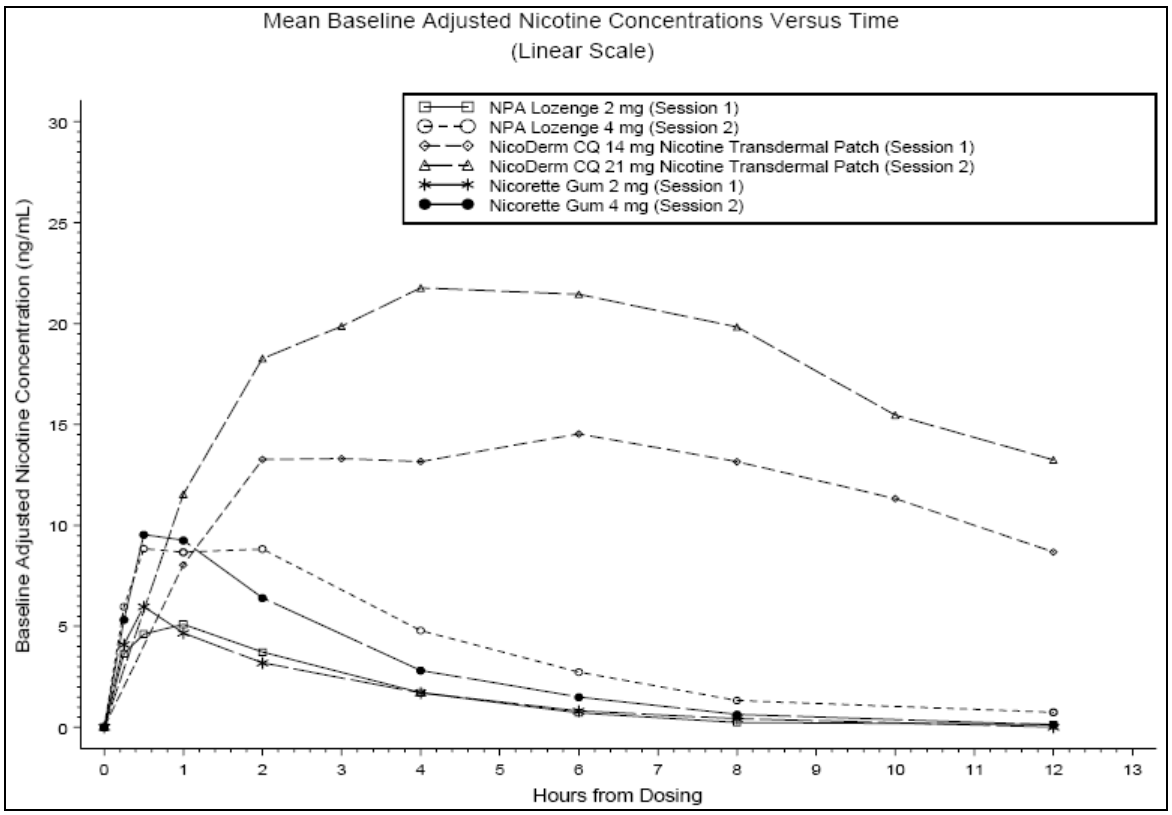
Treatment Group B

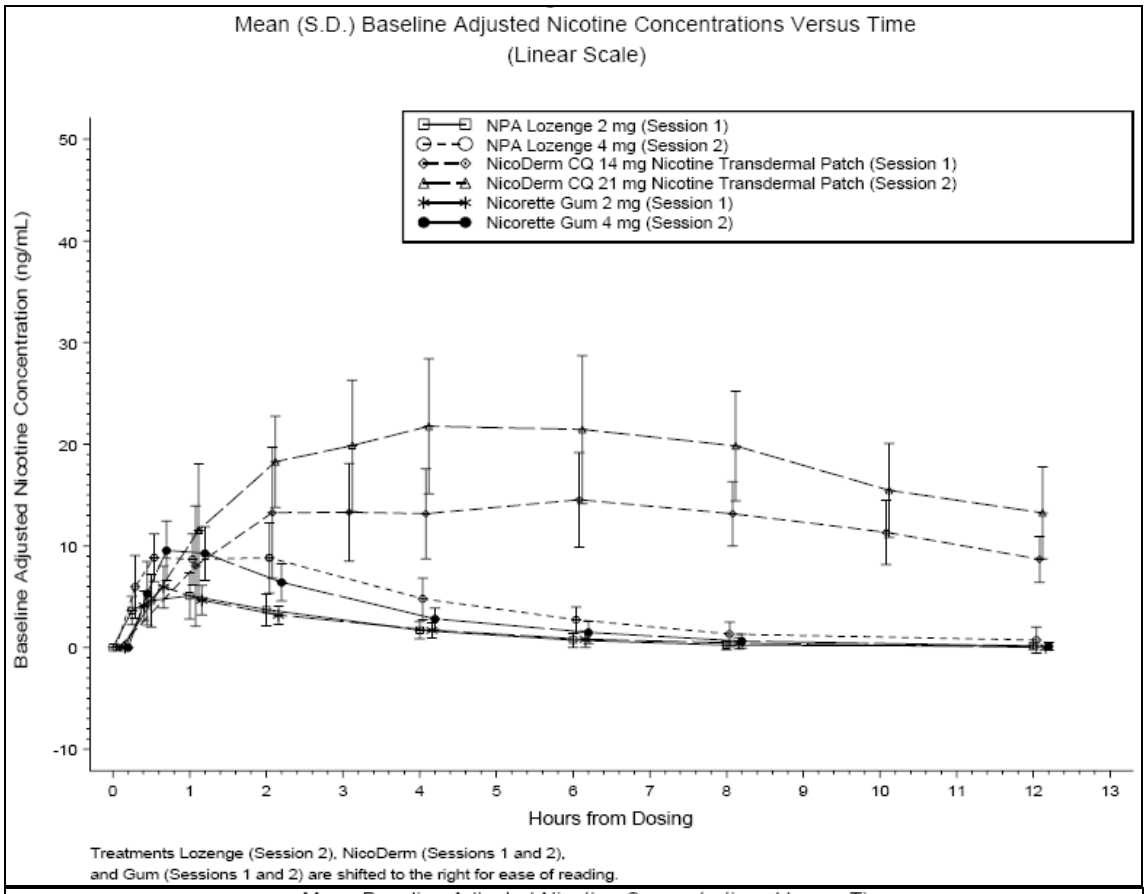
Age	Total N	Male subjects	Female subjects
13	2	0	2
14	3	1	2
15	1	0	1
16	1	1	0
17	8	5	3

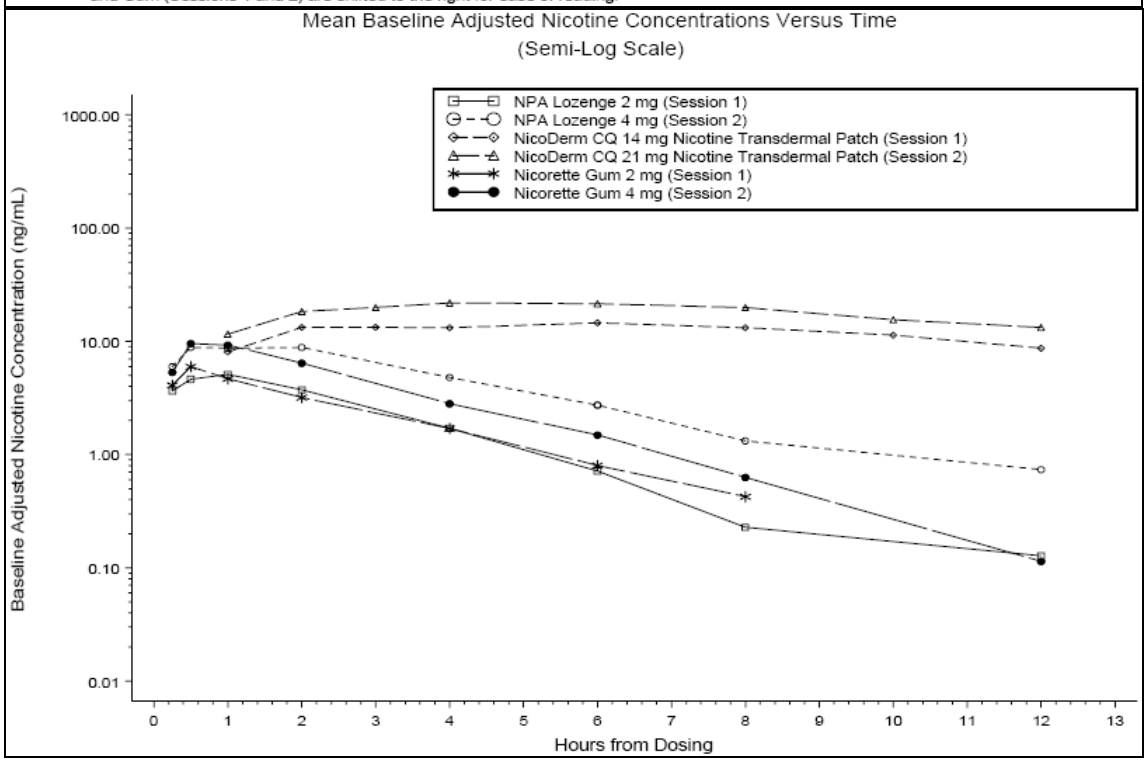
Treatment Group C

Age	Total N	Male subjects	Female subjects
13	2	1	1
14	1	1	0
15	3	1	2
16	5	1	4
17	4	2	2

2. Profiles




Mean (S.D.) Baseline Adjusted Nicotine Concentrations Versus Time
(Linear Scale)
NPA Lozenge 2 mg (Session 1)
NPA Lozenge 4 mg (Session 2)
NicoDerm CQ 14 mg Nicotine Transdermal Patch (Session 1)
NicoDerm CQ 21 mg Nicotine Transdermal Patch (Session 2)
Nicorette Gum 2 mg (Session 1)
Nicorette Gum 4 mg (Session 2)
Baseline Adjusted Nicotine Concentration (ng/mL)
50
40
30
20
10
0
-10
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Hours from Dosing
Treatments Lozenge (Session 2), NicoDerm (Sessions 1 and 2),
and Gum (Sessions 1 and 2) are shifted to the right for ease of reading.


Mean Baseline Adjusted Nicotine Concentrations Versus Time
(Semi-Log Scale)
NPA Lozenge 2 mg (Session 1)
NPA Lozenge 4 mg (Session 2)
NicoDerm CQ 14 mg Nicotine Transdermal Patch (Session 1)
NicoDerm CQ 21 mg Nicotine Transdermal Patch (Session 2)
Nicorette Gum 2 mg (Session 1)
Nicorette Gum 4 mg (Session 2)
Baseline Adjusted Nicotine Concentration (ng/mL)
1000.00
100.00
10.00
1.00
0.10
0.01
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Hours from Dosing

3. PK parameters

Table 5.1 Comparison of Baseline Adjusted Plasma Nicotine Pharmacokinetic Parameters Following NPA Lozenge 2 mg and 4 mg (Treatment A)

Plasma Nicotine

Parameters	4 mg NPA lozenge N	4 mg NPA lozenge Arithmetic Mean	4 mg NPA lozenge SD	2 mg NPA lozenge N	2 mg NPA lozenge Arithmetic Mean	2 mg NPA lozenge SD	90% CI#	% Mean Ratio#
Cmax (ng/ml)	8	11.091	2.094	13	5.395	2.455		
Tmax (hr)	8	1.16	0.738	12	1.09	0.466		
AUC (0-t) (ng*hr/ml)	8	43.68	17.35	13	16.65	7.204		
AUC (0-inf) (ng*hr/ml)	7	44.45	16.15	10	21.39	6.048		
T1/2 (hr)	7	2.36	0.709	10	1.99	0.436		
Kel (1/hr)	7	0.314	0.0831	10	0.367	0.0928		
ln (Cmax)	8	2.387	0.2202	12	1.720	0.3106	76.1-124.8	97.5
ln (AUC (0-t))	8	3.703	0.4160	12	2.845	0.3363	99.1-152.5	123.0
ln (AUC (0-inf))	7	3.737	0.3694	10	3.023	0.3099	80.7-135.9	104.7

Mean ratio and 90% CI are calculated from dose-normalized parameters.
Source: Tables 9.2.2.1.1, 9.2.2.1.2 and 9.2.3.1.

There was a slightly lower Cmax and higher AUC from 4 mg NPA lozenge compared to 2 mg lozenge.

Table 5.2 Comparison of Baseline Adjusted Plasma Nicotine Pharmacokinetic Parameters Following NicoDerm CQ 14 mg and 21 mg Nicotine Transdermal Patch (Treatment B)

Plasma Nicotine

Parameters	21 mg Nicoderm CQ N	21 mg Nicoderm CQ Arithmetic Mean	21 mg Nicoderm CQ SD	14 mg Nicoderm CQ N	14 mg Nicoderm CQ Arithmetic Mean	14 mg Nicoderm CQ SD	90% CI#	% Mean Ratio#
Cmax (ng/ml)	8	24.276	5.721	9	16.432	4.631		
Tmax (hr)	8	4.62	1.92	9	5.01	2.35		
AUC (0-t) (ng*hr/ml)	8	208.4	52.77	9	141.6	42.77		
AUC (0-inf) (ng*hr/ml)	7	327.8	114.5	8	227.6	67.24		
T1/2 (hr)	7	6.49	1.76	8	6.22	0.792		
Kel (1/hr)	7	0.114	0.0336	8	0.113	0.0155		
ln (Cmax)	8	3.165	0.2393	9	2.761	0.3010	86.5-125.3	104.1
ln (AUC (0-t))	8	5.313	0.2448	9	4.908	0.3281	93.3-123.1	107.2
ln (AUC (0-inf))	7	5.746	0.3202	8	5.381	0.3451	85.6-127.2	104.4

Mean ratio and 90% CI are calculated from dose-normalized parameters.
Source: Table 9.2.2.2.1, 9.2.2.2.2 and 9.2.3.2.

There was a slightly higher Cmax and AUC from 21 mg Nicoderm CQ® patch compared to 14 mg Nicoderm CQ® patch.

Table 5.3 Comparison of Baseline Adjusted Plasma Nicotine Pharmacokinetic Parameters Following Nicorette 2 mg and 4 mg Nicotine Gum (Treatment C)

Plasma Nicotine

Parameters	4 mg Nicorette Gum N	Arithmetic Mean	SD	2 mg Nicorette Gum N	Arithmetic Mean	SD	90% CI#	% Mean Ratio#
Cmax (ng/ml)	10	10.805	2.511	7	6.183	1.937		
Tmax (hr)	10	0.655	0.250	7	0.571	0.189		
AUC (0-t) (ng*hr/ml)	10	30.46	10.59	7	16.36	5.687		
AUC (0-inf) (ng*hr/ml)	10	34.93	11.66	7	19.72	5.987		
T1/2 (hr)	10	2.16	0.721	7	2.29	0.843		
Kel (1/hr)	10	0.362	0.141	7	0.339	0.124		
ln (Cmax)	10	2.354	0.2441	7	1.780	0.3134	70.6-116.4	90.7
ln (AUC (0-t))	10	3.350	0.4048	7	2.741	0.3576	84.6-121.7	101.4
ln (AUC (0-inf))	10	3.490	0.3980	7	2.942	0.3058	79.3-112.5	94.5

Mean ratio and 90% CI are calculated from dose-normalized parameters.
Source: Tables 9.2.2.3.1, 9.2.2.3.2 and 9.2.3.3.

There was a lower Cmax from 4 mg Nicorette® gum compared to 2 mg Nicorette® gum.

Bioanalytical summary

Analytical Study Report : A Pharmacokinetic and Safety Study of (b) (4) Nicotine Replacement Therapy Formulations in Adolescent Smokers (Protocol S1330074)

GlaxoSmithKline Consumer Healthcare 1500 Littleton Road, Parsippany, NJ 07054
Report Date: March 2002
Revised Report Date: November 2003

(b) (4)

Principal Scientist: (b) (6), BS

Objective: The analytical objective for this project was to perform analysis for nicotine and cotinine in human heparinized plasma in support of the overall study objectives.

Sample Analysis: Human heparinized plasma samples were analyzed for nicotine and cotinine concentrations by sensitive and specific LC-MS/MS procedures at (b) (4) (b) (4)

Analytical Method: A total of 6 analytical runs were required to process the nicotine clinical samples from this study. Of these 6 analytical runs, 5 were acceptable. Standard curves for the 5 analytical runs for human heparinized plasma used in this study covered a range of 1.00 to 50.00 ng/mL with a limit of quantitation of 1.00 ng/mL. Quality control samples analyzed with each analytical run had coefficients of variation less than or equal to 10.26%. A total of 5 analytical runs were required to process the cotinine clinical samples from this study. Of these 5 analytical runs, 5 were acceptable. Standard curves for the 5

analytical runs for human heparinized plasma used in this study covered a range of 10.00 to 500.00 ng/mL with a limit of quantitation of 10.00 ng/mL. Quality control samples analyzed with each analytical run had coefficients of variation less than or equal to 5.89%.

Linear Range
Nicotine: 1.0 - 50 ng/mL; Cotinine: 10 - 500 ng/mL

Limit of Quantitation
Nicotine: 1.0 ng/mL; Cotinine: 10 ng/mL

Precision and Accuracy

Interday

		Nicotine	
	QC 2.5 ng/mL	QC 15.0 ng/mL	QC 37.5 ng/mL
Mean	2.53	15.82	38.03
C.V.%	13.83	7.08	6.92
R.E.%	+1.20	+5.47	+1.41
N	30	30	30
		Cotinine	
	QC 25.0 ng/mL	QC 150.0 ng/mL	QC 375.0 ng/mL
Mean	25.01	161.29	387.26
C.V.%	10.00	9.81	8.31
R.E.%	+0.04	+7.53	+3.27
N	30	30	30

Intraday

		Nicotine	
	2.5 ng/mL	15.0 ng/mL	37.5 ng/mL
Mean	2.84	15.71	39.09
C.V.%	13.03	7.77	3.63
R.E.%	+13.60	+4.73	+4.24
N	6	6	6
		Cotinine	
	25.0 ng/mL	150.0 ng/mL	375.0 ng/mL
Mean	25.55	157.75	395.07
C.V.%	14.25	6.68	4.87
R.E.%	+2.20	+5.17	+5.35
N	6	6	6

Recovery and stability (reinjection/on-system stability, refrigeration, benchtop in the biological matrix, freeze/thaw cycles, and sample storage at -20 degree C) information was acceptable. There were no issues.

Validation Report: Validation of an LC/MS/MS Method for the Quantitation of Nicotine in Plasma

(b) (4)
Report Date: April 1997; Revised Report Date: April 1999; Revised Report Date: June 2000;

Revised Report Date: August 2001; Revised Report Date: October 2001

(b) (4)

Precision and Accuracy

1. Calibration Standards Interday Variation (ng/mL)

Nicotine					
	1.00	2.00	5.00	10.00	20.00
Mean C.V.% R.E.% N	0.95 8.42 -5.00 5	2.08 6.73 +4.00 4	5.00 5.20 +0.00 5	9.92 4.13 -0.80 5	21.07 3.23 +5.35 4
	25.00	40.00	50.00		
Mean C.V.% R.E.% N	24.90 4.14 -0.40 5	39.39 3.96 -1.53 5	49.91 2.81 -0.18 5		
Cotinine					
	10.0	20.0	50.0	100.0	200.0
Mean C.V.% R.E.% N	10.16 7.97 +1.60 5	19.65 4.43 -1.75 5	46.07 4.43 -7.86 3	104.47 5.80 +4.47 5	202.45 5.92 +1.22 5
	250.0	400.0	500.0		
Mean C.V.% R.E.% N	250.36 7.20 +0.14 5	400.22 3.63 +0.05 4	493.87 5.07 -1.23 4		

2. Quality Control Interday Variation (ng/mL)

		Nicotine	
	QC 2.5 ng/mL	QC 15.0 ng/mL	QC 37.5 ng/mL
Mean	2.53	15.82	38.03
C.V.%	13.83	7.08	6.92
R.E.%	+1.20	+5.47	+1.41
N	30	30	30
		Cotinine	
	QC 25.0 ng/mL	QC 150.0 ng/mL	QC 375.0 ng/mL
Mean	25.01	161.29	387.26
C.V.%	10.00	9.81	8.31
R.E.%	+0.04	+7.53	+3.27
N	30	30	30

3. Quality Control Intraday Variation (ng/mL)

		Nicotine	
	2.5 ng/mL	15.0 ng/mL	37.5 ng/mL
Mean	2.84	15.71	39.09
C.V.%	13.03	7.77	3.63
R.E.%	+13.60	+4.73	+4.24
N	6	6	6
		Cotinine	
	25.0 ng/mL	150.0 ng/mL	375.0 ng/mL
Mean	25.55	157.75	395.07
C.V.%	14.25	6.68	4.87
R.E.%	+2.20	+5.17	+5.35
N	6	6	6

Recovery and stability (reinjection/on-system stability, refrigeration, benchtop in the biological matrix, freeze/thaw cycles, and sample storage at -20 degree C) information was acceptable. There were no issues.

Reviewer's comments: The bioanalytical result is acceptable.

Appendix 1: Study report synopsis

Name of Company: GlaxoSmithKline Consumer Healthcare	**TABULAR FORMAT** **REFERRING TO PART OF THE DOSSIER** **Volume:** N/A **Page:** N/A	**(For National Authority Use Only)**
Name of Finished Products: NPA Nicotine Lozenge NicoDerm CQ® Nicotine Transdermal Patch Nicorette® Nicotine Gum		
Name of Active Substance: Nicotine		
Title of the study: A Pharmacokinetic and Safety Study of (b) (4) Nicotine Replacement Therapy Formulations in Adolescent Smokers		
Investigator: Philip Walson, MD Children's Hospital Medical Center 3333 Burnet Avenue Cincinnati, OH 45229-3039 USA		
Study center: Children's Hospital Medical Center 3333 Burnet Avenue Cincinnati, OH 45229-3039 USA		
Publication (reference): Not applicable.		
Studied period (years): August 2000 - December 2001	**Clinical Phase: I**	
Objective: The study objective was to characterize the pharmacokinetic profiles of the nicotine replacement therapy (NRT) formulations in adolescent smokers.		

Methodology:
This study was single-center, single-dose, open-label and dose-escalation in design. (b) (4) Subjects were enrolled in the following order of formulations: NPA Nicotine Lozenge, NicoDerm CQ Nicotine Transdermal Patch, and Nicorette Nicotine Gum. At Session One, the lower dose of assigned formulation was studied, i.e., lozenge (2 mg), patch (14 mg), or gum (2 mg).

At Session 2, the higher dose of assigned formulation was studied, i.e., lozenge (4 mg), patch (21 mg), or gum (4 mg). All subjects received nine blood draws over 12 hours relative to the dosing of the formulation for Sessions One and Two.

There was a wash-out period of at least 2 days between Sessions 1 and 2.

Number of Subjects (Total and for each Treatment):
A total of 72 subjects were planned to yield 48 evaluable subjects (b) (4) A total of 45 subjects were enrolled in the study and completed Session One treatment. Sixteen (16) subjects completed the 2 mg lozenge treatment, 14 subjects completed the 14 mg patch treatment, and 15 subjects completed the 2 mg gum treatment. A total of 37 subjects completed Session Two. Twelve (12) subjects completed the 4 mg lozenge treatment, 12 completed the 21 mg patch treatment, and 13 completed the 4 mg gum treatment.

Of the 45 subjects who were dosed, 37 subjects had evaluable pharmacokinetic data

Number of Subjects (Total and for each Treatment) (continued):

from at least one of the dosing sessions.

Diagnosis and Criteria for Inclusion:

Male and female subjects aged 10-17 years of age, who admitted to current cigarette smoking, the use of tobacco products, or the use of nicotine-containing substances were recruited to participate in this study.

Test Product, Dose, Mode of Administration, Batch No.:

- NPA Nicotine Lozenges; 2 mg (batch number: 9009FP-9009) and 4 mg (batch number: 9010FP-9008); administered orally as a single dose.
- NicoDerm CQ Nicotine Transdermal Patches; 14 mg (Lot numbers: 9L1604 and 0L2001) and 21 mg (Lot number: 0A0706); applied onto clean, dry skin which had minimal hair as a single dose.
- Nicorette Nicotine Gum 2 mg (Lot number: AL336A) and 4 mg (Lot number: AL280); administered orally as a single dose.

Duration of Treatment:

A single dose of one of the three test products was administered to each subject on two separate study days.

- Lozenges (2 mg and 4 mg) were moved from side to side of the mouth every four seconds until completely dissolved.
- Patches (14 mg and 21 mg) were applied to skin for 12 hours.

Duration of Treatment (continued):

- Gum (2 mg and 4 mg) was chewed once every four seconds, alternating the gum between both sides of the mouth every 30 seconds for a total of 30 minutes.

Criteria for Evaluation:

Pharmacokinetics:

The pharmacokinetics were assessed by measuring serial plasma nicotine concentrations after administration of 2 mg and 4 mg lozenges, 14 mg and 21 mg patches, and 2 mg and 4 mg gum.

The primary pharmacokinetic parameters C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$, and the secondary parameters T_{max}, $T_{1/2}$, and Kel were calculated for each study treatment session on baseline adjusted and unadjusted data.

The evaluation included an assessment of dose proportionality based on $ln[C_{max}/dose]$, $ln[AUC_{(0-t)}/dose]$, and $ln[AUC_{(0-inf)}/dose]$ values. Dose proportionality between the low and high doses with respect to $ln[C_{max}/dose]$, $ln[AUC_{(0-t)}/dose]$, and $ln[AUC_{(0-inf)}/dose]$ was concluded if the 90% confidence interval fell within the range of 80% to 125%. The statistical analysis was performed on baseline adjusted and unadjusted data. However, the final conclusions were based on results obtained from baseline adjusted data only.

Safety:

Assessment of safety included clinical signs and symptoms, adverse events (AEs),

Criteria for Evaluation (continued):

and clinical laboratories, including urinalysis, hematology, and serum chemistries.

Statistical Methods:

Summary statistics for all pharmacokinetic parameters were presented, and individual and mean plasma concentration-time profiles were provided. An adjustment for baseline was made for subjects with measurable nicotine in the predose samples. To assess dose proportionality between the low and high doses, an analysis of variance (ANOVA) model using SAS Proc Mixed was used on $ln[C_{max}/dose]$, $ln[AUC_{(0-t)}/dose]$, and $ln[AUC_{(0-inf)}/dose]$ values. The analysis included those subjects with data from at least one session. The factors in the analysis included subject and dose, with subject considered as a random effect. The two one-sided hypotheses were tested at the 5% level for $ln[C_{max}/dose]$, $ln[AUC_{(0-t)}/dose]$, and $ln[AUC_{(0-inf)}/dose]$ by constructing 90% confidence intervals for the ratio of means of the high and low doses. Dose proportionality between the low and high doses with respect to $ln[C_{max}/dose]$, $ln[AUC_{(0-t)}/dose]$, and $ln[AUC_{(0-inf)}/dose]$ was concluded if the 90% confidence interval fell within the range of 80% to 125%. The statistical analysis was performed on baseline adjusted and unadjusted data. However, the final conclusions were based on results obtained from baseline adjusted data only.

Procedures	Session 1		Washout	Session 2		End Of Study Assessment
	Baseline (12 hours immediately prior to Dosing)	Dosing	(at least two days)	Baseline (12 hours immediately prior to Dosing)	Dosing	
Inclusion/exclusion criteria	X			X		
Demographics & medical history	X*					
Physical examination	X*					
Electrocardiogram (12-lead)	X*					
Smoking history	X*					
Fagerstrom Test for Nicotine Dependence	X*					
Expired CO measurements	X	3x randomly[4]		X	3x randomly[4]	
Urine Test: pregnancy (if female), drug/alcohol screen	X[1]			X[1]		
Clinical safety laboratory tests	X			X		X
Dosing		X			X	
Blood samples for nicotine/cotinine[2]		X			X	
Meal record		X			X	
Review of current/concomitant med.	X	X----------→				
Adverse events	X	X[3]----------→				

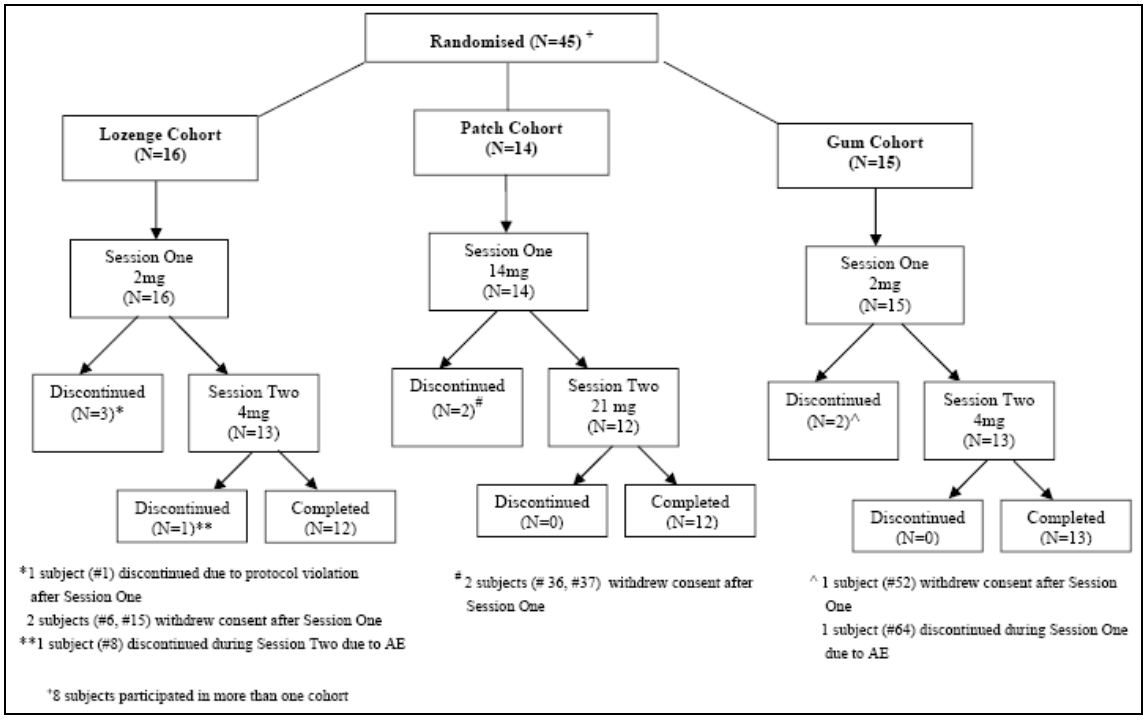
*These Procedures were scheduled to occur during the Screening Visit, which was collapsed to occur at Session 1, prior to the Baseline period, as per Protocol Amendment 1.

[1] Urine pregnancy, drug and alcohol screens were conducted so results were available prior to dosing.

[2] Blood samples were collected as follows: nicotine lozenge and gum cohorts: [0 (pre- dose), 0.25, 0.5, 1, 2, 4, 6, 8 and 12 hrs] , nicotine transdermal patch cohort [0 (pre-dose), 1, 2, 3, 4, 6, 8, 10 and 12 hours)].

[3] Adverse events considered by the investigator to have a relationship of probable or highly probable (to study medication), were to be followed to resolution. Adverse events ongoing at the final visit considered to have a relationship of possible, unlikely, or unrelated (to study medication) were to be followed to resolution or, if appropriate, documented in file notes.

[4] Each subject received 3 random CO measurements after dosing during each session.



*1 subject (#1) discontinued due to protocol violation after Session One
2 subjects (#6, #15) withdrew consent after Session One
**1 subject (#8) discontinued during Session Two due to AE

2 subjects (# 36, #37) withdrew consent after Session One

^ 1 subject (#52) withdrew consent after Session One
1 subject (#64) discontinued during Session One due to AE

+8 subjects participated in more than one cohort

SUMMARY – CONCLUSIONS:

Pharmacokinetic Results:

The arithmetic means of pharmacokinetic parameters of plasma nicotine and the statistical comparisons of these parameters following Treatments A (NPA lozenge 2 mg and 4 mg), B (NicoDerm CQ 14 mg and 21 mg nicotine transdermal patch), and C (Nicorette 2 mg and 4 mg nicotine gum) are summarized in the following tables.

Pharmacokinetic Results (continued):

Comparison of Baseline Adjusted Plasma Nicotine Pharmacokinetic Parameters Following NPA Lozenge 2 mg and 4 mg (Treatment A) Session Two Versus Session One

	Plasma Nicotine							
	4 mg NPA lozenge			2 mg NPA lozenge				
Parameters	N	Arithmetic Mean	SD	N	Arithmetic Mean	SD	90% CI#	% Mean Ratio#
Cmax (ng/ml)	8	11.091	2.094	13	5.395	2.455		
Tmax (hr)	8	1.16	0.738	12	1.09	0.466		
AUC (0-t) (ng*hr/ml)	8	43.68	17.35	13	16.65	7.204		
AUC (0-inf) (ng*hr/ml)	7	44.45	16.15	10	21.39	6.048		
T1/2 (hr)	7	2.36	0.709	10	1.99	0.436		
Kel (1/hr)	7	0.314	0.0831	10	0.367	0.0928		
ln (Cmax)	8	2.387	0.2202	12	1.720	0.3106	76.1-124.8	97.5
ln (AUC (0-t))	8	3.703	0.4160	12	2.845	0.3363	99.1-152.5	123.0
ln (AUC (0-inf))	7	3.737	0.3694	10	3.023	0.3099	80.7-135.9	104.7

Mean ratio and 90% CI are calculated from dose-normalized parameters.
Source: Tables 9.2.2.1.1, 9.2.2.1.2 and 9.2.3.1.

Comparison of Baseline Adjusted Plasma Nicotine Pharmacokinetic Parameters Following NicoDerm CQ 14 mg and 21 mg Nicotine Transdermal Patch (Treatment B) Session Two Versus One

	Plasma Nicotine							
	21 mg Nicoderm CQ			14 mg Nicoderm CQ				
Parameters	N	Arithmetic Mean	SD	N	Arithmetic Mean	SD	90% CI#	% Mean Ratio#
Cmax (ng/ml)	8	24.276	5.721	9	16.432	4.631		
Tmax (hr)	8	4.62	1.92	9	5.01	2.35		
AUC (0-t) (ng*hr/ml)	8	208.4	52.77	9	141.6	42.77		
AUC (0-inf) (ng*hr/ml)	7	327.8	114.5	8	227.6	67.24		
T1/2 (hr)	7	6.49	1.76	8	6.22	0.792		
Kel (1/hr)	7	0.114	0.0336	8	0.113	0.0155		
ln (Cmax)	8	3.165	0.2393	9	2.761	0.3010	86.5-125.3	104.1
ln (AUC (0-t))	8	5.313	0.2448	9	4.908	0.3281	93.3-123.1	107.2
ln (AUC (0-inf))	7	5.746	0.3202	8	5.381	0.3451	85.6-127.2	104.4

Mean ratio and 90% CI are calculated from dose-normalized parameters.
Source: Table 9.2.2.2.1, 9.2.2.2.2 and 9.2.3.2.

Comparison of Baseline Adjusted Plasma Nicotine Pharmacokinetic Parameters Following Nicorette 2 mg and 4 mg Nicotine Gum (Treatment C) Session Two Versus Session One

Plasma Nicotine

Parameters	4 mg Nicorette Gum N	Arithmetic Mean	SD	2 mg Nicorette Gum N	Arithmetic Mean	SD	90% CI#	% Mean Ratio#
Cmax (ng/ml)	10	10.805	2.511	7	6.183	1.937		
Tmax (hr)	10	0.655	0.250	7	0.571	0.189		
AUC (0-t) (ng*hr/ml)	10	30.46	10.59	7	16.36	5.687		
AUC (0-inf) (ng*hr/ml)	10	34.93	11.66	7	19.72	5.987		
T1/2 (hr)	10	2.16	0.721	7	2.29	0.843		
Kel (1/hr)	10	0.362	0.141	7	0.339	0.124		
ln (Cmax)	10	2.354	0.2441	7	1.780	0.3134	70.6-116.4	90.7
ln (AUC (0-t))	10	3.350	0.4048	7	2.741	0.3576	84.6-121.7	101.4
ln (AUC (0-inf))	10	3.490	0.3980	7	2.942	0.3058	79.3-112.5	94.5

Mean ratio and 90% CI are calculated from dose-normalized parameters.

Safety Results:

A total of 61 adverse events (AEs) were reported by 30 (67%) of the 45 subjects dosed during Session One. A total of 58 adverse events (AEs) were reported by 27 (69%) of the 39 subjects dosed during Session Two. The majority of the events in both sessions were mild in severity and no serious AEs occurred. One subject in each session was discontinued from the study due to AEs of nausea and/or vomiting. Nausea was the most frequently reported treatment-related AE in both sessions.

All three formulations were moderately well tolerated and the AE profiles observed were consistent with those previously observed in adult smokers. Regarding tolerability, a greater number of subjects reported AEs following the two Nicorette gum formulations than the patch or lozenge treatments. There were no trends in clinical laboratory results to suggest treatment-related differences.

Conclusions:

- The pharmacokinetic parameters of nicotine observed in adolescent smokers in this study were generally comparable to those reported in adult smokers in all three formulations studied.
- Lower and higher doses of NPA Nicotine Lozenge, NicoDerm CQ® patch, and Nicorette® gum did not show dose proportionality. Although no definite conclusions can be made from the pharmacokinetic data available due to the relative high variability and small sample size:

  There was a slightly lower rate of absorption and higher extent of absorption from 4 mg NPA lozenge compared to 2 mg lozenge.

Conclusions (continued):

There was a slightly higher rate and extent of absorption of nicotine from nicotine patch from 21 mg NicoDerm CQ® patch compared to 14 mg NicoDerm CQ® Patch.

There was a numerically lower rate of absorption and comparable AUC gum from 4 mg Nicorette® gum compared to 2 mg Nicorette® gum.

- The adult doses of NPA Nicotine Lozenge, NicoDerm CQ® patch, and Nicorette® gum were moderately well tolerated in adolescent smokers.

Date of Report: September 22, 2004

Study Medications:

Table 3.2 Study Medications

Cohort	Treatment	Dosage	Batch/LOT No.	Expiry Date 1	Expiry Date 2 (extended via memo)
1	Nicotine Lozenge	2 mg	9009FP-9009	Mar 2001	Sep 2001
	Nicotine Lozenge	4 mg	9010FP-9008	Mar 2001	Sep 2001
2	Nicotine Transdermal Patch	14 mg	9L1604	31 Oct 2001	
	Nicotine Transdermal Patch	14 mg	0L2001	30 Apr 2003	
	Nicotine Transdermal Patch	21 mg	0A0706	31 May 2002	
3	Nicotine Gum	2 mg	AL336A	31 May 2002	
	Nicotine Gum	4 mg	AL280	31 May 2002	

Demographics:

Data Listing 2.3
Subjects Excluded from Pharmacokinetic Analysis

Subject Number*	Treatment Group	Final Visit Date
8	A	31MAR2001
9	A	11MAR2001
31	B	04JUN2001
37	B	18AUG2001
39	B	08DEC2001
52	C	28AUG2001
58	C	29NOV2001
64	C	10DEC2001

Subject Number	Study Period	Treatment Group	First Medication Date	Birth date	Age (yrs)	Gender	Race	Height (in)	Weight (lb)
1	Screening	A	04DEC2000	(b) (6)	15	Female	Caucasian	65.5	160.9
2	Screening	A	09DEC2000		16	Female	Caucasian	67.0	125.2
3	Screening	A	08DEC2000		16	Male	Caucasian	66.5	140.0
4	Screening	A	13JAN2001		16	Male	Caucasian	69.2	143.8
5	Screening	A	17FEB2001		15	Female	Caucasian	64.9	143.9
6	Screening	A	17FEB2001		17	Female	Caucasian	60.9	106.3
7	Screening	A	24FEB2001		16	Male	Caucasian	70.9	141.9
8	Screening	A	23FEB2001		17	Male	Caucasian	67.7	134.8
9	Screening	A	25FEB2001		17	Female	Caucasian	60.1	112.4
10	Screening	A	03MAR2001		14	Male	Caucasian	61.1	103.4
11	Screening	A	10MAR2001		17	Male	Caucasian	66.4	138.6
12	Screening	A	10MAR2001		15	Male	Caucasian	68.4	165.4
13	Screening	A	25MAR2001		14	Female	Caucasian	66.2	129.4
14	Screening	A	25MAR2001		13	Female	Caucasian	63.0	102.1
15	Screening	A	11APR2001		16	Male	Caucasian	71.1	140.8
16	Screening	A	05JUN2001		17	Male	Caucasian	69.1	132.9
26	Screening	B	10APR2001		17	Male	Caucasian	68.5	143.7
27	Screening	B	29APR2001		15	Female	Caucasian	64.2	147.8
28	Screening	B	29APR2001		17	Female	Caucasian	59.7	114.0
29	Screening	B	12MAY2001		14	Female	Caucasian	64.0	131.0
30	Screening	B	28MAY2001		17	Male	Caucasian	66.4	137.5
	*Screening	B	08JUL2001		17	Male	Caucasian	66.6	138.0
31	Screening	B	31MAY2001		17	Male	Caucasian	69.5	157.0
32	Screening	B	08JUN2001		17	Male	Caucasian	66.5	121.7

Subject Number	Study Period	Treatment Group	First Medication Date	Birth date	Age (yrs)	Gender	Race	Height (in)	Weight (lb)
33	Screening	B	12JUN2001	(b) (6)	17	Female	Caucasian	62.0	150.0
34	Screening	B	17JUN2001		17	Female	Caucasian	61.2	131.8
35	Screening	B	21JUN2001		16	Male	Caucasian	69.3	141.0
36	Screening	B	14AUG2001		13	Female	Caucasian	62.1	125.0
37	Screening	B	14AUG2001		14	Female	Caucasian	63.5	131.7
38	Screening	B	20OCT2001		14	Male	Caucasian	64.0	129.2
39	Screening	B	01DEC2001		13	Female	Caucasian	62.0	132.0
51	Screening	C	26AUG2001		17	Male	Caucasian	69.0	151.8
52	Screening	C	28AUG2001		16	Male	Caucasian	66.1	141.1
53	Screening	C	02SEP2001		17	Female	Caucasian	61.5	134.7
54	Screening	C	08SEP2001		15	Female	Caucasian	63.4	124.6
55	Screening	C	07OCT2001		17	Male	Caucasian	68.2	154.7
56	Screening	C	30OCT2001		15	Female	Caucasian	67.4	172.0
57	Screening	C	04NOV2001		17	Female	Caucasian	66.6	119.0
58	Screening	C	27NOV2001		16	Female	Caucasian	68.9	165.7
59	Screening	C	01DEC2001		13	Female	Caucasian	61.2	112.9
60	Screening	C	01DEC2001		13	Male	Caucasian	65.0	114.5
61	Screening	C	01DEC2001		14	Male	Caucasian	64.5	117.7
62	Screening	C	04DEC2001		16	Female	Caucasian	64.6	153.4
63	Screening	C	04DEC2001		16	Female	Caucasian	65.9	140.9
64	Screening	C	10DEC2001		16	Female	Caucasian	62.4	111.1
65	Screening	C	16DEC2001		15	Male	Caucasian	64.3	126.1

Appendix 2: Analytical Study Report

Analytical Study Report : A Pharmacokinetic and Safety Study of (b) (4) Nicotine Replacement Therapy Formulations in Adolescent Smokers (Protocol S1330074)

GlaxoSmithKline Consumer Healthcare 1500 Littleton Road, Parsippany, NJ 07054
Report Date: March 2002; Revised Report Date: November 2003

(b) (4)

Principal Scientist: (b) (6), BS

Objective: The analytical objective for this project was to perform analysis for nicotine and cotinine in human heparinized plasma in support of the overall study objectives.

Sample Analysis: Human heparinized plasma samples were analyzed for nicotine and cotinine concentrations by sensitive and specific LC-MS/MS procedures at (b) (4), (b) (4)

Analytical Method: A total of 6 analytical runs were required to process the nicotine clinical samples from this study. Of these 6 analytical runs, 5 were acceptable. Standard curves for the 5 analytical runs for human heparinized plasma used in this study covered a range of 1.00 to 50.00 ng/mL with a limit of quantitation of 1.00 ng/mL. Quality control samples analyzed with each analytical run had coefficients of variation less than or equal to 10.26%. A total of 5 analytical runs were required to process the cotinine clinical samples from this study. Of these 5 analytical runs, 5 were acceptable. Standard curves for the 5 analytical runs for human heparinized plasma used in this study covered a range of 10.00 to 500.00 ng/mL with a limit of quantitation of 10.00 ng/mL. Quality control samples analyzed with each analytical run had coefficients of variation less than or equal to 5.89%.

Linear Range
Nicotine: 1.0 - 50 ng/mL; Cotinine: 10 - 500 ng/mL

Limit of Quantitation
Nicotine: 1.0 ng/mL; Cotinine: 10 ng/mL

Precision and Accuracy

Interday

		Nicotine	
	QC 2.5 ng/mL	QC 15.0 ng/mL	QC 37.5 ng/mL
Mean	2.53	15.82	38.03
C.V.%	13.83	7.08	6.92
R.E.%	+1.20	+5.47	+1.41
N	30	30	30
		Cotinine	
	QC 25.0 ng/mL	QC 150.0 ng/mL	QC 375.0 ng/mL
Mean	25.01	161.29	387.26
C.V.%	10.00	9.81	8.31
R.E.%	+0.04	+7.53	+3.27
N	30	30	30

Intraday

		Nicotine	
	2.5 ng/mL	15.0 ng/mL	37.5 ng/mL
Mean	2.84	15.71	39.09
C.V.%	13.03	7.77	3.63
R.E.%	+13.60	+4.73	+4.24
N	6	6	6
		Cotinine	
	25.0 ng/mL	150.0 ng/mL	375.0 ng/mL
Mean	25.55	157.75	395.07
C.V.%	14.25	6.68	4.87
R.E.%	+2.20	+5.17	+5.35
N	6	6	6

Recovery and stability (reinjection/on-system stability, refrigeration, benchtop in the biological matrix, freeze/thaw cycles, and sample storage at -20 degree C) information was acceptable. There were no issues.

Validation Report: Validation of an LC/MS/MS Method for the Quantitation of Nicotine in Plasma

(b) (4)

Report Date: April 1997; Revised Report Date: April 1999; Revised Report Date: June 2000; Revised Report Date: August 2001; Revised Report Date: October 2001

(b) (4)

Precision and Accuracy

1. Calibration Standards Interday Variation (ng/mL)

Nicotine					
	1.00	2.00	5.00	10.00	20.00
Mean C.V.% R.E.% N	0.95 8.42 -5.00 5	2.08 6.73 +4.00 4	5.00 5.20 +0.00 5	9.92 4.13 -0.80 5	21.07 3.23 +5.35 4
	25.00	40.00	50.00		
Mean C.V.% R.E.% N	24.90 4.14 -0.40 5	39.39 3.96 -1.53 5	49.91 2.81 -0.18 5		
Cotinine					
	10.0	20.0	50.0	100.0	200.0
Mean C.V.% R.E.% N	10.16 7.97 +1.60 5	19.65 4.43 -1.75 5	46.07 4.43 -7.86 3	104.47 5.80 +4.47 5	202.45 5.92 +1.22 5
	250.0	400.0	500.0		
Mean C.V.% R.E.% N	250.36 7.20 +0.14 5	400.22 3.63 +0.05 4	493.87 5.07 -1.23 4		

2. Quality Control Interday Variation (ng/mL)

		Nicotine	
	QC 2.5 ng/mL	QC 15.0 ng/mL	QC 37.5 ng/mL
Mean	2.53	15.82	38.03
C.V.%	13.83	7.08	6.92
R.E.%	+1.20	+5.47	+1.41
N	30	30	30
		Cotinine	
	QC 25.0 ng/mL	QC 150.0 ng/mL	QC 375.0 ng/mL
Mean	25.01	161.29	387.26
C.V.%	10.00	9.81	8.31
R.E.%	+0.04	+7.53	+3.27
N	30	30	30

3. Quality Control Intraday Variation (ng/mL)

		Nicotine	
	2.5 ng/mL	15.0 ng/mL	37.5 ng/mL
Mean	2.84	15.71	39.09
C.V.%	13.03	7.77	3.63
R.E.%	+13.60	+4.73	+4.24
N	6	6	6
		Cotinine	
	25.0 ng/mL	150.0 ng/mL	375.0 ng/mL
Mean	25.55	157.75	395.07
C.V.%	14.25	6.68	4.87
R.E.%	+2.20	+5.17	+5.35
N	6	6	6

Recovery and stability (reinjection/on-system stability, refrigeration, benchtop in the biological matrix, freeze/thaw cycles, and sample storage at -20 degree C) information was acceptable. There were no issues.

Appendix 3: OCP sNDA Filing and Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		**Information**
NDA/BLA Number	**21330 / S-013**	**Brand Name**	**Nicorette**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Nicotine polacrilex**
Medical Division	**OND/ODEIV/DNCE**	**Drug Class**	**Smoking cessation**
OCP Reviewer	**David Lee, Ph.D.**	**Indication(s)**	**Reduction of withdrawal symptoms, including Nicotine Craving associated with quitting smoking.**
OCP Team Leader	**Yun Xu, Ph.D.**	**Dosage Form**	**2 and 4 mg lozenge**
Pharmacometrics Reviewer		**Dosing Regimen**	**Weeks 1-6: 1 piece every 1 – 2 h; Weeks 7–9: 1 piece every 2 – 4h; Weeks 10-12: 1 piece every 4-8 h**
Date of Submission	**Mar 25, 2011**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**Mar 27, 2012**	**Sponsor**	**GlaxoSmithKline**
Medical Division Due Date	**Mar 27, 2012**	**Priority Classification**	**Standard; Efficacy supplement-Postmarketing Requirement: Pediatric Research Equity Act**
PDUFA Due Date	**May 29, 2012**		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	**x**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**x**	**1**		

geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				**See above description**
Literature References	**x**			**Clinical supportive information**
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			Analytical site: (b) (4) (b) (4)
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and	x			

	biopharmaceutics section of the NDA legible so that a substantive review can begin?				
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			The Applicant reference the 2007 submission;
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			**PK info to address Postmarketing Requirement: Pediatric Research Equity Act**
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	x			PK comparison data
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			x	
19	Was the translation (of study reports or other study information) from another			x	

	language needed and provided in this submission?				

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _____yes___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

GlaxoSmithKline (GSK) submitted a Supplement 013 in order to fulfill the PREA requirements. Reference was made to a pharmacokinetic pediatric study conducted in 2007 (NDA 21330 Submission date 8/20/07; Protocol S1330074; Title: A Pharmacokinetic and Safety Study of (b) (4) Nicotine Replacement Therapy Formulations in Adolescent Smokers). This submission was dated 3/25/11. However, PDUFA clock didn't start until 7/29/11 due to non payment of user-fee. For this supplement, the information in study report S1330074 will be reviewed.

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/s/

DAVID J LEE
03/26/2012

YUN XU
03/26/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		**Information**
NDA/BLA Number	**21330 / S-013**	**Brand Name**	**Nicorette**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Nicotine polacrilex**
Medical Division	**OND/ODEIV/DNCE**	**Drug Class**	**Smoking cessation**
OCP Reviewer	**David Lee, Ph.D.**	**Indication(s)**	**Reduction of withdrawal symptoms, including Nicotine Craving associated with quitting smoking.**
OCP Team Leader	**Yun Xu, Ph.D.**	**Dosage Form**	**2 and 4 mg lozenge**
Pharmacometrics Reviewer		**Dosing Regimen**	**Weeks 1-6: 1 piece every 1 – 2 h; Weeks 7–9: 1 piece every 2 – 4h; Weeks 10-12: 1 piece every 4-8 h**
Date of Submission	**Mar 25, 2011**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**Mar 27, 2012**	**Sponsor**	**GlaxoSmithKline**
Medical Division Due Date	**Mar 27, 2012**	**Priority Classification**	**Standard; Efficacy supplement-Postmarketing Requirement: Pediatric Research Equity Act**
PDUFA Due Date	**May 29, 2012**		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	**x**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**x**	**1**		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				**See above description**
Literature References	**x**			**Clinical supportive information**
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			Analytical site: (b) (4) (b) (4)
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to	x			

	begin?				
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			The Applicant reference the 2007 submission;
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			**PK info to address Postmarketing Requirement: Pediatric Research Equity Act**
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	x			PK comparison data
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this			x	

	product?				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____yes___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

GlaxoSmithKline (GSK) submitted a Supplement 013 in order to fulfill the PREA requirements. Reference was made to a pharmacokinetic pediatric study conducted in 2007 (NDA 21330 Submission date 8/20/07; Protocol S1330074; Title: A Pharmacokinetic and Safety Study of (b) (4) Nicotine Replacement Therapy Formulations in Adolescent Smokers). This submission was dated 3/25/11. However, PDUFA clock didn't start until 7/29/11 due to non payment of user-fee. For this supplement, the information in study report S1330074 will be reviewed.

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/s/

DAVID J LEE
09/27/2011

YUN XU
09/27/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21330/S-013

OTHER REVIEW(S)

Addendum Labeling Review for Nicorette Lozenge *Draft Labeling*

SUBMISSION DATES:	May 9, 2012
RELATED SUBMISSIONS:	February 10, 2012
NDA/SUBMISSION TYPE:	21330/S-013
ACTIVE INGREDIENTS:	Nicotine polacrilex 2 mg and 4 mg
SPONSOR:	Iris M. Shelton Associate Director, Regulatory Affairs GlaxoSmithKline Consumer Healthcare, L.P. 1500 Littleton Road Parsippany, NJ 07054-3884 Tel. 973-889-2100; FAX 973-889-2390 www.gsk.com
REVIEWER:	Mary S. Robinson, M.S. Regulatory Review Chemist
TEAM LEADER:	Colleen Rogers, Ph.D. Microbiologist

I. BACKGROUND

This review is based on GlaxoSmithKline Consumer Health Care's (GSKCH) submissions dated May 9, 2012 and February 10, 2012 requesting to add the following language under the "Directions" section of the Drug Facts label: "If you are under 18 years of age ask a doctor before use. No studies have been done to show if this product will work for you."

Reference is made to the FDA May 3, 2012 email requesting revision of the 189 count club pack net quantity statements for consistence with 21 CFR 201.62.

Reference is made to the May 4, 2012 phone discussion with the agency regarding the proposed alternative language, "if you are under 18 years of age, ask a doctor before use. No studies have been done to show this product will work for you" as also stated in the May 3, 2012 email. This language is proposed to be added to "Drug Facts", "Directions" section as a fulfillment of PREA requirements for the nicotine polacrilex lozenges, 2 mg and 4 mg.

This supplement contains revised "Drug Facts" labeling and a new package size label for the 189 count club pack. Mint is the only flavor that the sponsor proposes to market in this package size.

SKU SUBMITTED LABELING			
	72 Count	108 Count	189 Count
Original		2mg/4mg	
Mint	2mg/4mg		2mg/4mg
Cherry	2mg /4 mg		
Cappuccino	2mg/4mg		

The proposed labeling was compared to the currently approved labeling (August 27, 2010) that was approved as part of NDA 21330/S-009.

II. REVIEWER'S COMMENTS

The draft printed labeling (DPL) is identical to the approved labeling for the Nicorette lozenge 2 mg and 4 mg 72- and 108-count cartons with the exception of a revision to the directions section**.**

A. Outer Carton Drug Facts Label (Original 108-count, and Mint, Cherry, Cappuccino Flavors, 72-coun*t)*

i. Directions. The "Drug Facts" is the same as the approved labeling (August 27, 2010) with the exception of the following:

Under "Directions." The first bullet under the heading "Directions" is revised from "**if you are under 18 years of age, ask a doctor before use**" to read "**if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.**"

This is acceptable.

***B*. 189-Count club pack.**

The club pack is formatted as a large backer card to which 7 poppac containers are attached using a clear plastic blister. The top third of the front of the backer card contains the same elements as the PDP of the 72-count carton.

i. Front card.

a. Top right and bottom right portion of the front card contains the following net quantity statement:

"189 Lozenges
2 mg/4 mg Each"
(7 Poppac Containers of 27)

This is acceptable.

ii. Back card

a. Drug Facts, Directions. The "Drug Facts" is the same as the approved labeling (August 27, 2010) with the exception of the following:

The first bullet under the heading "Directions" is revised from "**if you are under 18 years of age, ask a doctor before use**" to read "**if you are under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you.**"

This is acceptable.

III. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted 2 mg and 4 mg Nicorette lozenge flavor variants (original, mint, cherry, cappuccino) labeling and request final printed labeling. Request that the sponsor submit final printed labeling (FPL) identical to: 27-count mint immediate container (vial) label submitted on February 10, 2012, and the 72-count mint, cherry and cappuccino carton labels, the 108-count original carton label, and the 189-count mint "club pack" backer card (front and back panels) submitted on May 9, 2012.

Even though no revisions were made to the consumer information leaflet (User's Guide (booklet or leaflet format)) or the immediate container (27-count vial and 12-count blister card), the approval letter should request that the sponsor submit these labels as part of the FPL for this supplement in order to maintain a record of the complete labeling (count sizes and packaging configurations) being approved as part of this supplement .

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

Following this page, 12 pages withheld in full - draft labeling (b)(4)

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/s/

MARY S ROBINSON
05/17/2012

COLLEEN K ROGERS
05/17/2012

Labeling Review for Nicorette Lozenge
Draft Labeling

SUBMISSION DATES:	February 10, 2012, January 31, 2012
RELATED SUBMISSIONS:	September 8, 2011, September 7, 2011, August 9, 2011, April 21, 2011, April 15, 2011, March 25 2011
NDA/SUBMISSION TYPE:	21330/S-013
ACTIVE INGREDIENTS:	Nicotine polacrilex 2 mg and 4 mg
SPONSOR:	Iris M. Shelton Associate Director, Regulatory Affairs GlaxoSmithKline Consumer Healthcare, L.P. 1500 Littleton Road Parsippany, NJ 07054-3884 Tel. 973-889-2100; FAX 973-889-2390 www.gsk.com
REVIEWER:	Mary S. Robinson, M.S. Regulatory Review Chemist
TEAM LEADER:	Colleen Rogers, Ph.D. Microbiologist

I. BACKGROUND

This review is based on GlaxoSmithKline Consumer Health Care's (GSKCH) submissions dated January 31, 2012 and February 10, 2012 requesting the addition of the following language in "Directions" section of the Drug Facts label: "If you are under 18 years of age ask a doctor before use. (b) (4) ."

Reference is made to the March 25, 2011 (as amended April 15, April 21, August 9, September 7, September 8) submission in which GSKCH submitted as a fulfillment of PREA requirements for the nicotine polacrilex lozenges, 2 mg and 4 mg.

Reference is also made to the April 15 2011 submission containing representative labeling that incorporates the proposed statement requested by the FDA on April 5 2011:

> "if you are under 18 years of age ask a doctor before use. (b) (4) (b) (4) ."

Reference is made to the April 21, 2011 submission listing all of the proposed SKUs to be marketed as request in the FDA email of April 18, 2011:

Reference is made to the FDA letter of October 11, 2011 requesting additional information regarding packaging and labeling.

This supplement contains a new package size, the 189 count club pack. Reference is made to the February 10, 2012 submission in response to FDA Email request of February 9, 2012 stating that the approval request for the 189 count club pack labeling for the Nicorette Mint lozenge was provided in the amendment of January 31, 2012. Mint is the only flavor that the sponsor proposes to market in this package size.

The sponsor also states that this submission contains the 27 count immediate containers (Poppac) labels for the mint lozenges. This vial is identical to that approved for the 24 count product, including the same text (approval letter of 10/25/05).

The sponsor states that no changes are made to the currently approved User's Guide and the immediate container labeling. The only change made is to the carton labeling for each flavor variant.

SKU Submitted Labeling				
Proposed Nicorette Lozenge Packages				
	27 Count vials	72 Count	108 Count	189 Count
Original			2mg/4mg	
Mint	2mg/4mg	2mg/4mg		2mg/4mg
Cherry		2mg /4 mg		
Cappuccino		2mg/4mg		

The proposed labeling was compared to the currently approved labeling (August 27, 2010) that was approved as part of NDA 21330/S-009.

II. REVIEWER'S COMMENTS

The draft printed labeling (DPL) is identical to the approved labeling for the Nicorette lozenge 2 mg and 4 mg 72- and 108-count cartons, 24-count vial products and User Guide with the exception of a revision to the directions section.

A. Carton Principal Display Panel (PDP) (Original 108-count, and Mint, Cherry, Cappuccino Flavors, 72-count).

i. The words "Previously Commit" are deleted from the top right corner.

This is acceptable.

B. Outer Carton Drug Facts Label (Original 108-count, and Mint, Cherry, Cappuccino Flavors, 72-coun*t)*

i. Directions. The "Drug Facts" is the same as the approved labeling (August 27, 2010) with the exception of the following:

Under "Directions." The first bullet under the heading "Directions" is revised from "if you are under 18 years of age, ask a doctor before use" to read "if you are under 18 years of age, ask a doctor before use. (b) (4) (b) (4) "

The acceptability and/or revision of this statement is deferred to DNCE for evaluation and sponsor negotiation.

C. **Immediate Container Label, 27-Count Vial**.

i. Three lozenges are added to the 24 count vial (approved October 25, 2005) to make a 27 count vial. The labeling is the same with exception to the new count size.

This is acceptable. On March 22, 2012, I spoke with Jim Vidra (CMC) regarding approval of the 27 count vial. He stated that if the container and the materials of construction were the same as the 24 count vial there should be no safety concerns. The sponsor stated that the 27-count vial is identical to the 24-count vial. The labeling for the 27-count vial is identical to the currently approved 24-count vial with the exception of the count size.

D. 189-Count club pack.
The club pack is formatted as a large backer card to which 7 poppac containers are attached using a clear plastic blister. The top third of the front of the backer card contains the same elements as the PDP of the 72-count carton.

i. Front card.
a. The labeling for the 189-count club pack contains the same sunburst design as the other Nicorette packaging approved labeling (August 27, 2010).

This is acc*eptable.*

b. Top left portion of the front card is the same as the approved PDP labeling (August 27, 2010) for the 72- count carton. This area contains the trade name, statement of identity, and indication. Below that is the strength (2 mg/4 mg) and statement "for those who smoke their first cigarette…"

This is acceptable.

c. Top right corner the mint flavor graphic icon is added

This is acceptable.

d. Top right and bottom right portion of the front card contains the following net quantity statement:

"189 Lozenges
(7 Poppac Containers of 27)
2 mg/4 mg Each"

This is not acceptable. Revise the phrases at the top and bottom right for consistency with 21 CFR 201.62 and other Nicorette packaging as follows:

"189 Lozenges
2 mg/4 mg Each
(7 Poppac Containers of 27)"

ii. Back card

a. Top left portion of the back card is the same as the approved (August 27, 2010) PDP labeling top portion for the 72- count carton. This area contains the trade name, statement of identity, and indication.

This is acceptable.

b. The approved Nicorette Poppac graphic opening icon and directions are place on the top right.

This is acceptable.

c. The personalized Quit plan information is placed in the upper middle of the back card.

This is acceptable.

d. Directions. The "Drug Facts" is the same as the approved labeling (August 27, 2010) with the exception of the following:

The first bullet under the heading "Directions" is revised from "if you are under 18 years of age, ask a doctor before use" to read "if you are under 18 years of age, ask a doctor before use. (b) (4) (b) (4)."

The acceptability and/or revision of this statement is deferred to DNCE for evaluation and sponsor negotiation.

e. Below the Drug Facts box on the left side is the "to increase your success in quitting" language. Below this is the tamper evident statement.

This is acceptable.

f. Below the Drug Facts box on the right side is a red box containing the "not for sale" statements. Below the red box is the trademark information and distributor information.

This is acceptable.

g. The lot and expiration date area is located on the lower right corner.

This is acceptable.

E. Consumer Information Leaflet or Package Insert

i. The User's Guide was not submitted, however, the sponsor states (January 31, 2011) that no changes were made to the User's Guide.

This is acceptable.

III. RECOMMENDATIONS

We currently recommend a Complete Response action pending the resolution of the following labeling deficiencies:

- For the 189-count club pack, revise the net quantity statements on the PDP (both top and bottom) for consistency with 21 CFR 201.62 and other Nicorette packaging as follows:

  "189 Lozenges
  2 mg/4 mg Each
  (7 Poppac Containers of 27)"

IV. SUBMITTED LABELING

The labels on the remaining pages of this labeling review were submitted and evaluated in this labeling review:

Following this page, 16 pages withheld in full - draft labeling (b)(4)

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/s/

MARY S ROBINSON
04/11/2012

COLLEEN K ROGERS
04/12/2012

Filing Checklist for Nicorette Lozenges

SUBMISSION DATES:	April 15 and April 21, 2011
NDA/SUBMISSION TYPE:	21330/S-013
RELATED SUBMISSION	March 25, 2010
ACTIVE INGREDIENTS:	2 mg and 4 mg Nicotine Polacrilex gum
SPONSOR:	Iris H. Shelton Assicuate Director, Regulatory Affairs GlaxoSmithKline Consumer Healthcare, L.P.
REVIEWER:	Mary S. Robinson, Regulatory Review Chemist
TEAM LEADER:	Colleen K. Rogers, PhD., Microbiologist

Submitted Labeling		**Representative of Following SKUs**	
Flavor	**Count**	**Count**	
	108	72	168
Original	2 mg/4mg		
Mint		2 mg/4 mg	2 mg/4mg
Cherry		2 mg/4mg	

	Yes/No	Comments
Is the supplement correctly assigned as a PA, CBE0, CBE30?	Yes	
Are the outer container and immediate container labels, and consumer information leaflet and other labeling included for all submitted SKUs?	No	Representative labeling only; Only outer cartons provided
If representative labeling is submitted, does the submitted labeling represent only SKUs of different count sizes (same flavor and dosage form)?	No	Different flavors
Is distributor labeling included?	No	
Does the submission include the annotated specifications for the Drug Facts label?	No	
Is Drug Facts title and Active ingredient/Purpose section of Drug Facts label visible at time of purchase?	Yes	
Do any of the labels include "prescription strength" or similar statements?	No	
Do any of the labels include "#1 doctor recommended" or similar endorsement statements?	No	
Do any labels include text in a language other than English?	No	
Is a new trade name being proposed? If multiple trade names, is the primary or preferred trade name identified?	No	
Does a medical officer need to review any clinical issues?	No	
If SLR, should ONDQA also review?		

An information request is necessary.
Please ask the sponsor to submit the following information:

- **consumer information leaflet (user guide)**
- **Cartons (or representative cartons) for each flavor variant. Representative labeling can be for different count sizes only.**
- **Drug Facts specifications**
- **Confirmation that there are no changes to the immediate container**

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/s/

MARY S ROBINSON
09/19/2011

COLLEEN K ROGERS
09/19/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21330/S-013

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 021330 SUPPL # 013 HFD #

Trade Name Nicorette lozenge

Generic Name nicotine polacrilex

Applicant Name GlaxoSmithKline Consumer Healthcare

Approval Date, If Known 5/23/12

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2), SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Labeling change to satisfy PREA PMR showing effectiveness has not been studied in pediatric populations. Language to be added to the Drug Facts label: "if you under 18 years of age, ask a doctor before use. No studies have been done to show if this product will work for you."

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20536 Nicotrol patch

NDA# 18612 Nicorette gum

NDA# 20066 Nicorette gum

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
 !

IND # YES ☐ ! NO ☐
 ! Explain:

Investigation #2 !
 !

IND # YES ☐ ! NO ☐
 ! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
 !

YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Phong Do
Title: Regulatory Project Manager, DNCE
Date: 5/24/12

Name of Office/Division Director signing form: Joel Schiffenbauer
Title: Deputy Directory, DNCE

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

PHONG DO
05/24/2012

JOEL SCHIFFENBAUER
05/24/2012

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 021330 BLA #	NDA Supplement # 013 BLA Supplement #	If NDA, Efficacy Supplement Type: Labeling change w/ clinical data
Proprietary Name: Nicorette Established/Proper Name: nicotine polacrilex Dosage Form: lozenge		Applicant: GlaxoSmithKline Consumer Healthcare LP Agent for Applicant (if applicable):
RPM: Phong Do		Division: Division of Nonprescription Clinical Evaluation

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☒ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

NDA 20536 Nicotrol Patch

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☒ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: 5/22/12

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 5/29/12	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☒ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	5/24/12
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) 5/22/12
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Over-the-counter medication
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☐ DMEPA ☐ DMPP/PLT (DRISK) ☐ ODPD (DDMAC) ☐ SEALD ☐ CSS ☒ Other reviews DNRD 4/12/12, 5/17/12
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	10/11/11
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☐ Not a (b)(2) 5/14/12
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☐ Not a (b)(2) 5/24/12
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 5/2/12 If PeRC review not necessary, explain: ____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☐ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	5/19/11; 8/23/11; 9/2/11; 10/11/11; 11/21/11;11/23/11; 2/9/12; 3/8/12; 5/3/12
❖ Internal memoranda, telecons, etc.	5/20/11
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 5/23/12
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 5/5/12
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	5/5/12
• Clinical review(s) *(indicate date for each review)*	4/11/12 DNCE; 4/11/12 DAAAP
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None

[6] Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 3/26/12
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☐ None requested
Product Quality ☒ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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/s/

PHONG DO
05/24/2012

505(b)(2) ASSESSMENT

Application Information		
NDA # 21330	NDA Supplement #: S- 013	Efficacy Supplement Type SE- 8
Proprietary Name: Nicorette Established/Proper Name: nicotine polacrilex Dosage Form: lozenge Strengths: 2 mg & 4 mg		
Applicant: GlaxoSmithKline Consumer Healthcare		
Date of Receipt: July 29, 2011		
PDUFA Goal Date: May 29, 2012	Action Goal Date (if different):	
Proposed Indication(s): Reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published literature	Efficacy and safety data
Nicotrol Patch NDA 020536	Efficacy

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The sponsor's reliance on published literature demonstrates that efficacy studies in the pediatric population could not be adequately performed.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

Nicotrol Patch

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

Appears this way on original.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Nicotrol patch	NDA#20536	y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☒ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*

*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing: Nicotrol patch

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").
This application provides for new labeling, "If you are under 18 years of age, ask a doctor before use. (b) (4)". This is to satisfy their PREA PMR

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO ☒

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):Approved generics are listed in the Orange book.

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☒ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): Nicotrol patch NDA#20536 Patent#?

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

PHONG DO
05/24/2012

Memo

Application: NDA 21330/S-013
Applicant: GlaxoSmithKline
Drug Product: Nicorette Polacrilex Lozenge 2 mg and 4 mg
Date of Submission: 8/9/2011

This memo to file is regarding Nicotrol Transdermal Patch 15 mg, a product of McNeil Consumer Healthcare, which was the active drug product used in some of the literature studies referenced in this NDA supplement submission. Nicotrol Patch 15 mg was approved for OTC marketing on July 3, 1996. As noted in the Annual Reports, distribution of this product was discontinued in July 2002 subsequent to the approval of the 3-step Nicotine Transdermal System under NDA 20-150/S001. Production was discontinued to avoid duplicate marketing of the 15 mg transdermal patch and was not related to concerns about product safety or efficacy.

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/s/

PRISCILLA C LYON
05/15/2012

DAIVA SHETTY
05/15/2012

From:	Do, Phong
To:	"Iris Shelton"
Subject:	NDA 21330/S-013; Nicorette lozenge; Labeling comments
Date:	Thursday, May 03, 2012 4:05:00 PM

Dear Ms. Shelton,

Please refer to your March 25, 2011 Supplemental New Drug Application (sNDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Nicorette (nicotine polacrilex) lozenge, 2 mg and 4 mg.

We also refer to our October 11, 2011 letter in which we notified you of our target date of May 1, 2012 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES - FISCAL YEARS 2008 THROUGH 2012."

We have received your April 15, 2011, January 31 and February 12, 2012 submissions to this application containing proposed labeling. We have the following proposed revisions and request a response by COB May 7, 2012:

1. On the Drug Facts section under "Directions" - add the following:

- if you are under 18 years of of age, ask a doctor before use. No studies have been done to show this product will work for you.

2. For the 189-count club pack, revise the net quantity statements on the PDP (both top and bottom) for consistency with 21 CFR 201.62 and other Nicorette packaging as follows:

“189 Lozenges
2 mg/4 mg Each
(7 Poppac Containers of 27)”

Labeling should be revised and resubmitted for our review and comment. Please confirm receipt of this email.

Thank you,

Phong Do, PharmD
Lieutenant - USPHS
Regulatory Project Manager
FDA/CDER/ODEIV/DNCE
Phone 301-796-4795

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/s/

PHONG DO
05/03/2012

Do, Phong

From: Lee, James C.
Sent: Tuesday, April 17, 2012 9:40 AM
To: Do, Phong
Subject: FW: NDA 21330 s/13
Follow Up Flag: Follow up
Flag Status: Red

LT James Lee, PharmD.
United States Public Health Service
Regulatory Project Manager
FDA-CDER-ODEIV
Division of Nonprescription Clinical Evaluation
10903 New Hampshire Avenue, Bldg. 22, Room 5471
Silver Spring, MD 20903
Tel: 301-796-5283 Fax: 301-796-9850
Email: james.lee4@fda hhs.gov

From: Lee, James C.
Sent: Thursday, March 08, 2012 1:35 PM
To: 'iris.h.shelton@gsk.com'
Subject: NDA 21330 s/13

Dear Ms. Shelton,

Please refer to your Supplemental New Drug Application (sNDA) dated March 25, 2011, received July 29, 2011, for Nicorette (nicotine polacrilex) lozenge, 2 mg and 4 mg.

We also refer to your amendment dated January 31, 2012.

In this submission you provided a revised FDA form 356h indicating this supplement is submitted under section 505(b)(2). Please resubmit form 356h as a formal amendment to the supplement to include identification of an appropriate reference listed drug(s). Please note the regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each reference listed drug upon which an applicant relies.

In this submission you also provided a Paragraph II Patent Certification for McNeil's Nicotrol products referred to in the Killen 2001 study. Please clarify where McNeil's Nicotrol product is specifically cited in this study and how it relates to your product.

Best Regards,
James Lee

LT James Lee, PharmD.
United States Public Health Service
Regulatory Project Manager
FDA-CDER-ODEIV
Division of Nonprescription Clinical Evaluation
10903 New Hampshire Avenue, Bldg. 22, Room 5471
Silver Spring, MD 20903
Tel: 301-796-5283 Fax: 301-796-9850
Email: james.lee4@fda hhs.gov

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/s/

PHONG DO
04/17/2012

From:	Do, Phong
To:	"Iris Shelton"
Subject:	NDA 21330/S-013; Nicorette Lozenge; Information Request
Date:	Thursday, February 09, 2012 1:19:00 PM

Dear Ms. Shelton,

Please refer to your Supplemental New Drug Application (sNDA) dated March 25, 2011, received July 29, 2011, for Nicorette (nicotine polacrilex) lozenge, 2 mg and 4 mg.

We also refer to your amendment dated January 31, 2012.

We have the following requests for information:

1. Please submit the following new pieces of labeling for review, or provide the supplement number and action date of the approval:

- 189 count club pack back card (front and back panels)
- 27 count immediate container (poppac)

2. Please clarify whether the labels submitted on Jan 31, 2012 are representative labels or whether they represent all pieces of labeling proposed to be marketed with the changes proposed in this supplement. If the submitted labeling is representative labeling, please specify what the representative labeling represents. Please note that representative labeling is only acceptable when the only difference in the labels is the count size.

Confirm receipt of this email and respond to this information request by COB Wednesday, February 15, 2012.

Thank you
Phong Do, PharmD
Lieutenant - USPHS
Regulatory Project Manager
FDA/CDER/ODEIV/DNCE
Phone 301-796-4795

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/s/

PHONG DO
02/09/2012

Do, Phong

From: Do, Phong
Sent: Wednesday, November 23, 2011 3:36 PM
To: 'Iris Shelton'
Subject: NDA 21330/S-013; Nicorette (nicotine polacrilex) lozenge, 2 and 4 mg; Information Request

Dear Ms. Shelton,

Please refer to your Supplemental New Drug Application (sNDA) dated March 25, 2011, received July 29, 2011, for Nicorette (nicotine polacrilex) lozenge, 2 mg and 4 mg.

Please also refer to your post marketing requirement (PMR) #493-3 associated with this sNDA:

PMR 493-3 - For the marketing of Commit™ (nicotine polacrilex lozenge), to reduce withdrawal symptoms, including nicotine craving, associated with quitting smoking, we are deferring submission of pediatric studies for patients 10-17 years until October 31, 2007. We are waiving the pediatric study requirement for this application for patients under age 10.

We request that you address the PMR for data for adolescent smokers aged 10-12 years old, since the PMR waiver only pertains to data for children under 10 years of age. You may either submit efficacy/safety/PK data for Nicorette in this age group or provide written justification for the waiver and evidence to support the request, e.g. additional evidence of impossibility or impracticality as to why children in this age group would be difficult to recruit/retain in any clinical trials to assess NRT products. You may be able to qualify for a partial waiver under one of the two conditions: 1) Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed) (section 505B(a)(4)(A)(i) of the Act), OR 2) There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in this pediatric age group (section 505B(a)(4)(A)(ii) of the Act).

Please confirm receipt of this email and provide an estimated submission date in response to this specific information request.

Also, as we indicated in a previous email sent to you (dated November 21, 2011), our information request conveyed to you on October 11, 2011 remains outstanding. In order for the review of this supplemental application to move forward, please also provide an estimated submission date for your responses to our October 11, 2011 request.

Thank you,

Phong Do, PharmD

Lieutenant - USPHS

Regulatory Project Manager
FDA/CDER/ODEIV/DNCE
Phone 301-796-4795

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/s/

PHONG D DO
11/23/2011

Do, Phong

From: Do, Phong
Sent: Monday, November 21, 2011 4:15 PM
To: 'Iris Shelton'
Subject: NDA 21330/S-013; Information Request

Follow Up Flag: Follow up
Flag Status: Red

Dear Ms. Shelton,

We request that you provide an estimated submission date in response to the Agency's comments from the letter dated October 11, 2011 regarding NDA 21330/Supplement - 013.

Please confirm receipt of this email.

Thank you,

Phong Do, PharmD

Lieutenant - USPHS

Regulatory Project Manager
FDA/CDER/ODEIV/DNCE
Phone 301-796-4795

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/s/

PHONG D DO
11/21/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021330/S-013

FILING COMMUNICATION

GlaxoSmithKline Consumer Healthcare, L.P.
Attention: Iris H. Shelton
Associate Director, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Ms. Shelton:

Please refer to your Supplemental New Drug Application (sNDA) dated March 25, 2011, received July 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nicorette (nicotine polacrilex) lozenge, 2 mg and 4 mg.

We also refer to your amendments dated April 15, April 21, August 9, September 7, and September 8, 2011.

This supplemental application proposes the addition of the following language in the "Directions" section of the Drug Facts label:

"If you are under 18 years of age, ask a doctor before use. (b) (4) (b) (4)"

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is May 29, 2012.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 1, 2012.

During our filing review of your supplemental application, we identified the following potential review issues and request that you submit the following information:

1. Provide an Integrated Summary of Safety on NRT use in adolescents, which should include:
    - An analysis of all adverse events reported to the postmarketing safety database concerning individuals under the age of 18. These events should be summarized using MedDRA coding. The time frame for the summary can be limited to the period from October 31, 2007 to October 30, 2010, to correspond to the last three periodic safety reports.
    - A summary of safety data from clinical studies (including the literature cited and S1330074).

2. Per 21 CFR 54 and 21 CFR 314.50, you are required to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. We were unable to locate this information in your submission. Please either clarify where this information is located within your submission or submit this information for the investigators involved in study S1330074.

3. We are unclear if you are proposing any changes to your consumer information leaflet (user guide). If you are, please submit your proposed changes. If you are not, please submit a statement that clarifies that you are proposing no changes to this piece of labeling.

4. Provide carton labeling for each flavor variant that you intend to market with the proposed change. Please note that representative labeling can only differ in count size from the labeling it represents.

5. Provide Drug Facts font specifications.

6. We are unclear if you are proposing any changes to your immediate container labeling. If you are, please submit your proposed changes. If you are not, please submit a statement that clarifies that you are proposing no changes to this piece of labeling.

7. You have submitted NDA 21-330/S-013 and identified it as a 505(b)(1) supplement, although this supplemental application relies on published literature. Please note that, as described in FDA's Guidance for Industry, *Applications Covered by Section 505(b)(2)*, an applicant should submit a 505(b)(2) application if approval of the application will rely ***to any extent*** on published literature. The guidance goes on to explain that if the applicant has not obtained a right of reference to the raw data underlying the published study or studies, the application is a 505(b)(2) application. *(We note that if the raw data are in the public domain, because, for example, the study was publicly funded, a right of reference is not needed, but note further that a study and its underlying data are not considered to be in the public domain simply because the study is published.)*

If you have obtained a right of reference to the raw data underlying the published studies that are needed to support approval of this supplemental application, please provide copies of letters ***from the sponsors of the studies*** authorizing the right to reference the raw data.

If you have not obtained a right of reference to the raw data underlying the published studies that are needed to support approval of this supplemental application, please submit a revised Form FDA 356h indicating that this supplement is submitted under section 505(b)(2). If this supplemental application relies on published literature describing a listed drug(s), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which an applicant relies.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the supplemental application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

If you have any questions, call Phong Do, Regulatory Project Manager, at (301) 796-4795.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, M.D., M.S.
Director
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

ANDREA LEONARD SEGAL
10/11/2011

Do, Phong

From: Erin Oliver [Erin.E.Oliver@gsk.com]
Sent: Friday, September 02, 2011 9:46 AM
To: Do, Phong
Cc: Iris Shelton
Subject: RE: NDA 21330/S-013; Information Request

Phong,

Thank you for your prompt response. We'll address the information request as described in your e-mail below.

Enjoy your holiday!

Regards.

Erin

From: Do, Phong [mailto:Phong.Do@fda.hhs.gov]
Sent: Friday, September 02, 2011 9:33 AM
To: Erin Oliver
Cc: Iris Shelton
Subject: FW: NDA 21330/S-013; Information Request

Hello Erin,

Iris' out of office message stated you're covering for her until Sep 6. I left her a voicemail yesterday telling her I'd send this info request out today.

Have a nice Labor Day

Phong

From: Do, Phong
Sent: Friday, September 02, 2011 9:23 AM
To: 'Iris Shelton'
Subject: NDA 21330/S-013; Information Request

Hello Iris,

I refer you to your August 31, 2011 voicemail and to our August 31, 2011 telephone conversation regarding sNDA 21330/Supplement 13. During that conversation you clarified your statement, "Please be advised that for those data included in this submission, they were either provided by the investigators to GSK directly or by letter of authorization from the sponsor."

Please submit, as an amendment to this supplement, your clarifications of where the data submitted to this supplement originated and if those studies were sponsored by GlaxoSmithKline (GSK) . Clarify what agreements GSK has with owners of data from studies not conducted by GSK.

Submit a response to this information request by COB Tuesday , September 6, 2011.

Please confirm receipt of this email.

Best Regards,
Phong Do, PharmD
Lieutenant - USPHS
Regulatory Project Manager
FDA/CDER/ODEIV/DNCE
Phone 301-796-4795

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/s/

PHONG D DO
09/02/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021330/S-013

PRIOR APPROVAL SUPPLEMENT
USER FEES RECEIVED

GlaxoSmithKline Consumer Healthcare, L.P.
Attention: Iris H. Shelton
Associate Director, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Ms. Shelton:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nicorette (nicotine polacrilex) lozenge, 2 mg and 4 mg.

You were notified in our letter dated May 19, 2011 that your supplemental application was not accepted for filing due to non-payment of fees. This is to inform you that the Agency has received all required fees and your application has been accepted as of July 29, 2011.

This supplemental application proposes the following change:

The addition of labeling information for patients under 18 years of age. This change proposes to include the statement, "If you are under 18 years of age, ask a doctor before use. (b) (4) (b) (4)" on the "Directions" section of the Drug Facts label.

In addition, we acknowledge your assertion that this submission fulfills your postmarketing requirement #0493-03 agreement associated with NDA 021330.

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 26, 2011 in accordance with 21 CFR 314.101(a).

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory

registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 021330/S-013** submitted on March 25, 2011 and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The application number cited above should be included at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Phong Do, Regulatory Project Manager, at (301) 796-4795.

Sincerely,

{See appended electronic signature page}

Melissa Hancock Furness
Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

MELISSA H FURNESS
08/23/2011

MEMORANDUM OF TELECON

DATE: May 20, 2011

APPLICATION NUMBER: NDA 021330/S-013 – Nicorette (nicotine polacrilex) lozenge, 2 mg and 4 mg

BETWEEN:

Name: Erin Oliver, Director Regulatory Affairs
David Schifkovitz, Vice President, Regulatory Affairs
Iris Shelton, Associate Director, Regulatory Affairs
(b) (6)

Representing: GlaxoSmithKline Consumer Healthcare

AND

Name: Andrea Leonard-Segal, M.D., M.S., Joel Schiffenbauer, M.D., Daiva Shetty M.D., Christina Chang M.D., Melissa Furness, Mike Jones, Phong Do

Phone: 866-803-2146
Division of Nonprescription Clinical Evaluation, HFD-560

SUBJECT: UNACCEPTABLE FOR FILING & DISCUSSION OF PDUFA FEE ASSESSMENT

DNCE informed the sponsor that the supplement submitted to the NDA is considered unacceptable for filing due to non-receipt of an appropriate user fee. The following reasons for the unacceptable for filing decision were communicated to the sponsor:

1. Any supplement requiring clinical data for approval requires the appropriate user fee paid before review of the application can begin.

2. The supplement submitted March 25, 2011 to NDA 021330 require FDA review of the clinical data submitted to the application.

The sponsor was notified of two options:

1. The sponsor may pay the fee and proceed with the supplement. The amount of the user fee to be assessed is subject to what fiscal year the sponsor submits the fee.

2. The sponsor may not pay the fee and the supplement will not proceed.

Phong Do, Regulatory Project Manager

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/s/

PHONG D DO
05/20/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021330/S-013 **UNACCEPTABLE FOR FILING**

GlaxoSmithKline Consumer Healthcare, L.P.
Attention: Iris H. Shelton
Associate Director, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Ms. Shelton:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Nicorette (nicotine polacrilex) lozenge, 2 mg and 4 mg

NDA Number: 021330

Supplement Number: 013

Date of Application: March 25, 2011

Date of Receipt: March 25, 2011

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 979107
St. Louis, MO 63197-9000

Checks sent by courier should be addressed to:

U.S. Bank
Attention: Government Lockbox 979107
1005 Convention Plaza
St. Louis, MO 63101

When submitting payment for an application fee, include the User Fee I.D. Number, the Application number, and a copy of the user fee coversheet (Form 3397) with your

application fee payment. When submitting payment for previously unpaid product and establishment fees, please include the Invoice Number(s) for the unpaid fees and the summary portion of the invoice(s) with your payment. The FDA P.O. Box number (P.O. Box 979107) should be included on any check you submit.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you wish to send payment by wire transfer, or if you have any other questions, please call Bev Friedman or Mike Jones at 301-796-3602.

If you have any questions, call Phong Do, Regulatory Project Manager, at (301) 796-4795.

Sincerely,

{See appended electronic signature page}

Melissa Hancock Furness
Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

MELISSA H FURNESS
05/19/2011