CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-330/S-21

Trade Name:	Nicorette
Generic or Proper Name:	nicotine polacrilex
Sponsor:	GlaxoSmithKline Consumer Healthcare
Approval Date:	August 10, 2018
Indication:	provides for a new mint flavor coated lozenge

CENTER FOR DRUG EVALUATION AND RESEARCH

NDA 21-330/S-21

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Reviews / Information Included in this NDA Review.

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Other Action Letters	
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Cross Discipline Team Leader Review	
Clinical Review	**X**
Chemistry Review	
Environmental Assessment	
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-330/S-21

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021330/S-021

SUPPLEMENT APPROVAL

GlaxoSmithKline Consumer Healthcare
Attention: Julia Kim
Senior Director, US Regulatory Affairs
184 Liberty Corner Road, Suite 200
Warren, NJ 07059

Dear Ms. Kim:

Please refer to your Supplemental New Drug Application (sNDA) dated and received February 22, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nicorette (nicotine polacrilex) lozenges, 2 mg and 4 mg.

We acknowledge receipt of your major amendment dated June 5, 2018, which extended the goal date by two months.

This "Prior Approval" sNDA provides for a new mint flavor coated lozenge which will be referred to as "Coated Ice Mint".

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

LABELING

Submit final printed labeling (FPL), as soon as they are available, but no more than 30 days after they are printed. The FPL must be identical to the labels and labeling listed in the table below, and must be in the "Drug Facts" format (21 CFR 201.66), where applicable.

Submitted Labeling	Date(s) Submitted
20-ct, 2 mg Immediate container "Flip-Pack" (front)	February 22, 2018
20-ct, 4 mg Immediate container "Flip Pack" (front)	February 22, 2018
20-ct, 2 mg and 4 mg Immediate container "Flip-Pack" (back)	February 22, 2018
20-ct, 2 mg outer carton container backer card (back)	February 22, 2018

20-ct, 2 mg outer carton container backer card (front)	June 25, 2018
20-ct, 4 mg outer carton container backer card (back)	February 22, 2018
20-ct, 4 mg outer carton container backer card (front)	June 25, 2018
80-ct (4x20 pack), 2 mg outer carton container backer card (back)	February 22, 2018
80-ct (4x20 pack), 2 mg outer carton container backer card (front)	June 25, 2018
80-ct (4x20 pack), 4 mg outer carton container backer card (back)	February 22, 2018
80-ct (4x20 pack), 4 mg outer carton container backer card (front)	June 25, 2018
120-ct (6x20 pack), 2 mg Club pack outer carton container backer card (front and back)	June 25, 2018
120-ct (6x20 pack), 4 mg Club pack outer carton container backer card (front and back)	June 25, 2018
Consumer Information leaflet (User's Guide leaflet)	February 22, 2018

The FPL should be submitted electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3).* For administrative purposes, designate this submission "**Final Printed Labeling for approved NDA 21330/S-021**." 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 Alina Salvatore, Regulatory Project Manager, at (240) 402-0379.

Sincerely,

{See appended electronic signature page}

Theresa Michele, MD
Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE(S):
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

THERESA M MICHELE
08/10/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

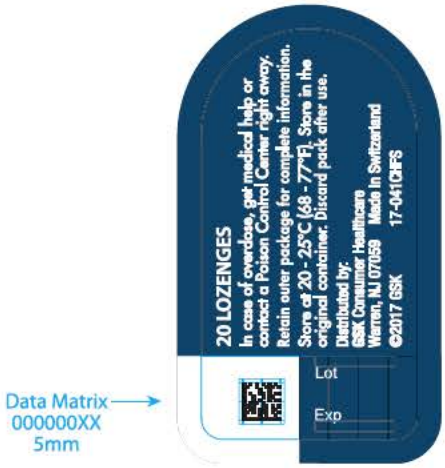
APPLICATION NUMBER:

NDA 21-330/S-21

LABELING

GSK Regulatory Spec Box				Verified Date: 9/25/17
Drug Facts Info				
Drug Facts (Title)	Font Name:			N/A
Drug Facts (continued)	Font Name:			N/A
Headings	Font Name:			N/A
Subheadings	Font Name:			N/A
Body text	Font Name:			N/A
Bullets	Font Name:			N/A
Bullets on same lines: end of statement separated from bulleted statement by two ems				N/A
Spacing of the hair lines from edge of box – i.e. Minimum of 2 spaces either side of Drug Fact Box				N/A
Tracking		N/A	Horizontal Scale:	N/A
Leading (Minimum space in body copy of Drug Facts)		N/A	Maximum Characters/Inch:	N/A
Barlines		N/A	Hairlines	N/A
Primary Display Panel Info				
Font size of Net Wt/Contents (Smallest character height in inches)				0.0943 in.
PDP dimensions (in square inches)				2.4 sq. in.
Font size of Statement of Identity (If not live text, to be measured in Helvetica capital "M")			V 6 pt.	H N/A pt.
Font size of Logo/Largest Copy on PDP (If not live text, to be measured in Helvetica capital "M")			V 15.4 pt.	H N/A pt.
Ratio of Statement of Identity to Logo/Largest Copy on PDP Statement of Identity (pt.) (Divided by) Largest Logo Copy (pt.)			V 38.9%	H N/A%

GSK Regulatory Spec Box				Verified Date: 9/25/17
Drug Facts Info				
Drug Facts (Title)	Font Name:			N/A
Drug Facts (continued)	Font Name:			N/A
Headings	Font Name:			N/A
Subheadings	Font Name:			N/A
Body text	Font Name:			N/A
Bullets	Font Name:			N/A
Bullets on same lines: end of statement separated from bulleted statement by two ems				N/A
Spacing of the hair lines from edge of box – i.e. Minimum of 2 spaces either side of Drug Fact Box				N/A
Tracking		N/A	Horizontal Scale:	N/A
Leading (Minimum space in body copy of Drug Facts)		N/A	Maximum Characters/Inch:	N/A
Barlines		N/A	Hairlines	N/A
Primary Display Panel Info				
Font size of Net Wt/Contents (Smallest character height in inches)				0.0943 in.
PDP dimensions (in square inches)				2.4 sq. in.
Font size of Statement of Identity (If not live text, to be measured in Helvetica capital "M")			V 6 pt.	H N/A pt.
Font size of Logo/Largest Copy on PDP (If not live text, to be measured in Helvetica capital "M")			V 15.4 pt.	H N/A pt.
Ratio of Statement of Identity to Logo/Largest Copy on PDP Statement of Identity (pt.) (Divided by) Largest Logo Copy (pt.)			V 38.9%	H N/A%



GSK Regulatory Spec Box				Verified Date: 9/29/17
Drug Facts Info				
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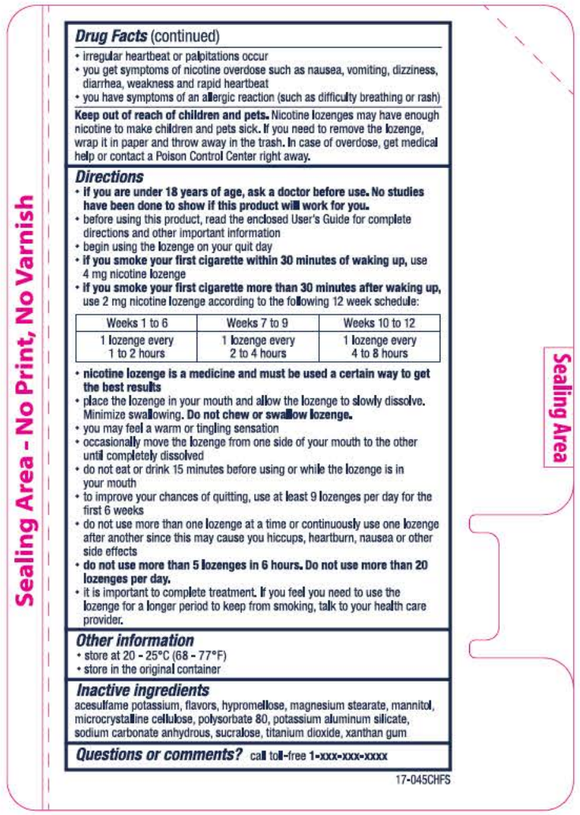
Headings	Font Name:			N/A point type
Subheadings	Font Name:			N/A point type
Body text	Font Name:			N/A point type
Bullets	Font Name:			N/A point type
Bullets on same lines: end of statement separated from bulleted statement by two ems				N/A
Spacing of the hair lines from edge of box – i.e. Minimum of 2 spaces either side of Drug Fact Box				N/A
Tracking	N/A	Horizontal Scale:		N/A
Leading (Minimum space in body copy of Drug Facts)	N/A pt.	Maximum Characters/Inch:		N/A
Barlines	N/A pt.	Hairlines		N/A pt.
Primary Display Panel Info				
Font size of Net Wt/Contents (Smallest character height in inches)				N/A in.
PDP dimensions (in square inches)				N/A sq. in.
Font size of Statement of Identity (If not live text, to be measured in Helvetica capital "M")			V N/A pt.	H N/A pt.
Font size of Logo/Largest Copy on PDP (If not live text, to be measured in Helvetica capital "M")			V N/A pt.	H N/A pt.
Ratio of Statement of Identity to Logo/Largest Copy on PDP Statement of Identity (pt.) (Divided by) Largest Logo Copy (pt.)			V N/A%	H N/A%

Inside of card coated side



Sealing Area - No Print, No Varnish

Sealing Area

Drug Facts (continued)

- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat
- you have symptoms of an allergic reaction (such as difficulty breathing or rash)

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
- begin using the lozenge on your quit day
- **if you smoke your first cigarette within 30 minutes of waking up,** use 4 mg nicotine lozenge
- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2 mg 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. 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
- 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.**
- it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.

Other information

- store at 20 - 25°C (68 - 77°F)
- store in the original container

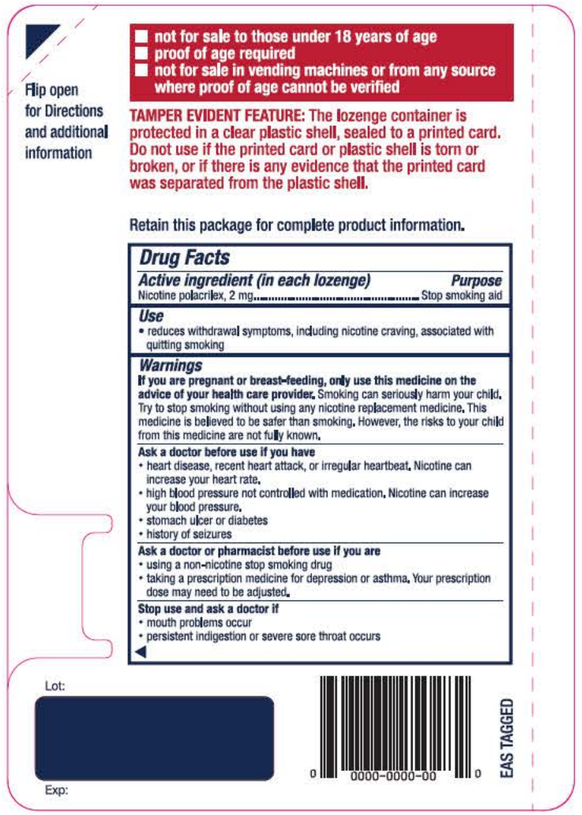
Inactive ingredients

acesulfame potassium, flavors, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, polysorbate 80, potassium aluminum silicate, sodium carbonate anhydrous, sucralose, titanium dioxide, xanthan gum

Questions or comments? call toll-free 1-xxx-xxx-xxxx

17-045CHFS

Outside of card, facing product (coated side)



Flip open for Directions and additional information

- **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: The lozenge container is protected in a clear plastic shell, sealed to a printed card. Do not use if the printed card or plastic shell is torn or broken, or if there is any evidence that the printed card was separated from the plastic shell.

Retain this package for complete product information.

Drug Facts

Active ingredient (in each lozenge)	***Purpose***
Nicotine polacrilex, 2 mg	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.

Ask a doctor before use if you have

- 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
- history of seizures

Ask a doctor or pharmacist before use if you are

- using a non-nicotine stop smoking drug
- taking a 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

Lot:

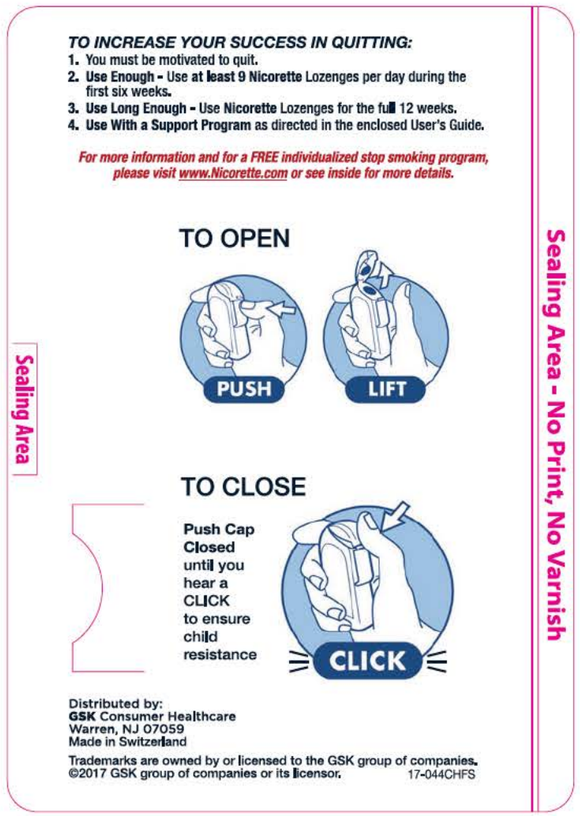
Exp:

0 0000-0000-00 0

EAS TAGGED

GSK Regulatory Spec Box			**Verified Date: 9.28.17**
Drug Facts Info			
Drug Facts (Title)	Font Name: Helvetica Neue LT Std 77 Bold Condensed Oblique		10 point type
Drug Facts (continued)	Font Name: Helvetica Neue LT Std 77 Bold Condensed Oblique/ Helvetica Neue LT Std 57 Condensed		8 point type
Headings	Font Name: Helvetica Neue LT Std 77 Bold Condensed Oblique		8 point type
Subheading	Font Name: Helvetica Neue LT Std 77 Bold Condensed		6 point type
Body text	Font Name: Helvetica Neue LT Std 77 Bold Condensed / Helvetica Neue LT Std 57 Condensed		6 point type
Bullets	Font Name: Helvetica Neue LT Std 55 Roman		5 point type
Bullets on same lines: end of statement separated from bulleted statement by two ems			Yes
Spacing of the hair lines from edge of box – i.e. Minimum of 2 spaces either side of Drug Fact Box			Yes
Tracking	0	Horizontal Scale:	97%-100%
Leading (Minimum space in body copy of Drug Facts)	6.5 pt.	Maximum Characters/Inch:	35
Barlines	1.5 pt.	Hairlines	0.50 pt.
Primary Display Panel Info			
Font size of Net Wt/Contents (Smallest character height in inches)			N/A
PDP dimensions (in square inches)			N/A
Font size of Statement of Identity (If not live text, to be measured in Helvetica capital "M")		N/A	N/A
Font size of Logo/Largest Copy on PDP (If not live text, to be measured in Helvetica capital "M")		N/A	N/A
Ratio of Statement of Identity to Logo/Largest Copy on PDP			
Statement of Identity (pt.) (Divided by) Largest Logo Copy (pt.)		N/A	N/A

Inside of card die-cut side



Outside of card, facing product (coated side)

GSK Regulatory Spec Box			Verified Date: 6.21.18
Drug Facts Info			
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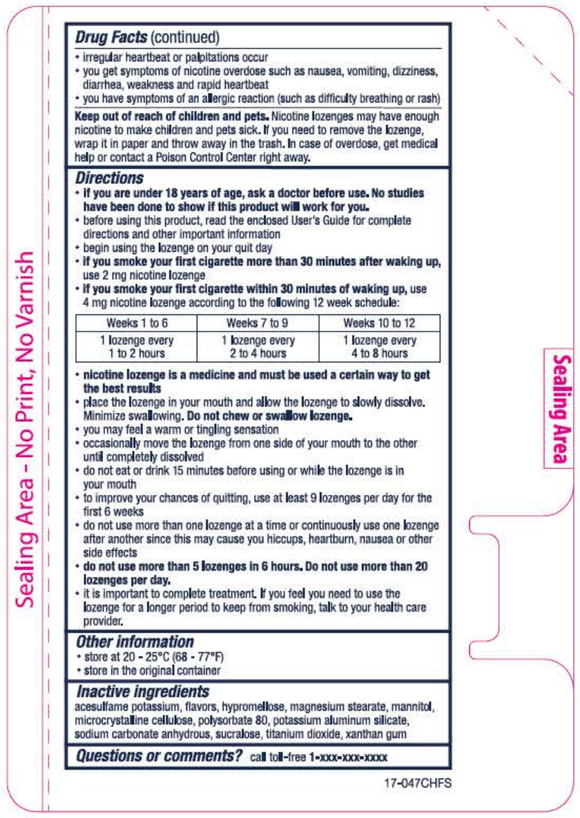
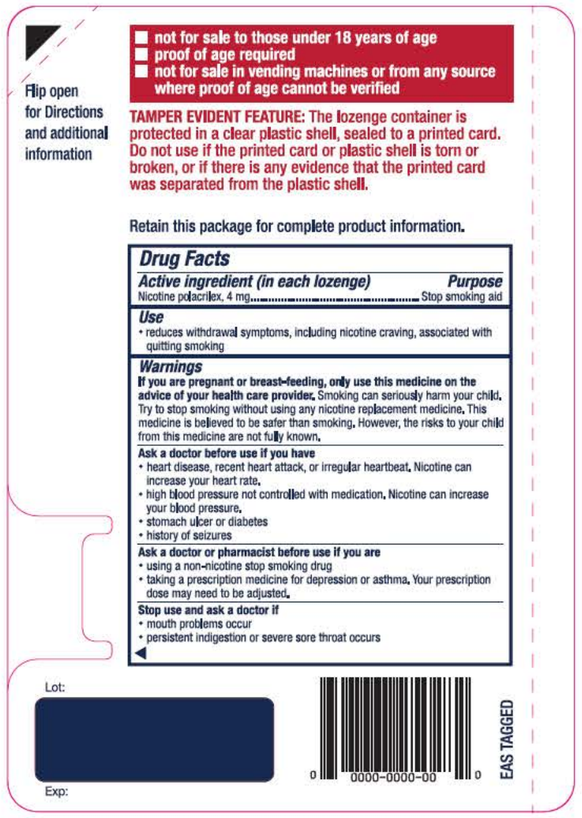
Drug Facts (continued)	Font Name: N/A		N/A point type
Headings	Font Name: N/A		N/A point type
Subheadings	Font Name: N/A		N/A point type
Body text	Font Name: N/A		N/A point type
Bullets	Font Name: N/A		N/A point type
Bullets on same lines: end of statement separated from bulleted statement by two ems			N/A
Spacing of the hair lines from edge of box – i.e. Minimum of 2 spaces either side of Drug Fact Box			N/A
Tracking	N/A	Horizontal Scale:	N/A
Leading (Minimum space in body copy of Drug Facts)	N/A pt.	Maximum Characters/Inch:	N/A
Barlines	N/A pt.	Hairlines	N/A pt.
Primary Display Panel Info			
Font size of Net Wt/Contents (Smallest character height in inches)			0.1624 in.
PDP dimensions (in square inches)			19.9 sq. in.
Font size of Statement of Identity (If not live text, to be measured in Helvetica capital "M")		V 13.3 pt.	H 0.00 pt.
Font size of Logo/Largest Copy on PDP (If not live text, to be measured in Helvetica capital "M")		V 46.0 pt.	H 0.00 pt.
Ratio of Statement of Identity to Logo/Largest Copy on PDP			
Statement of Identity (pt.) (Divided by) Largest Logo Copy (pt.)		V 28.9%	H 0%

Inside of card coated side



Outside of card, facing product (coated side)



GSK Regulatory Spec Box			Verified Date: 09.28.17
Drug Facts Info			
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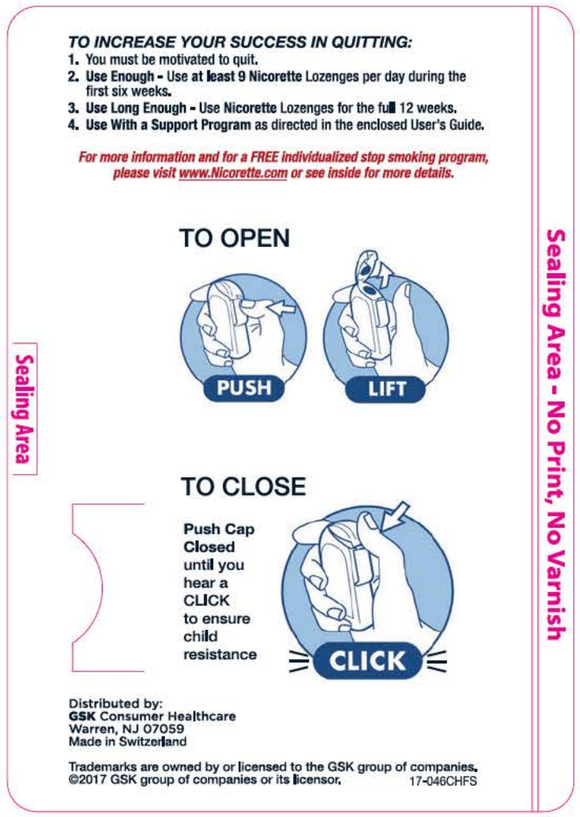
Headings	Font Name: Helvetica Neue LT Std 77 Bold Condensed Oblique		8 point type
Subheading	Font Name: Helvetica Neue LT Std 77 Bold Condensed		6 point type
Body text	Font Name: Helvetica Neue LT Std 77 Bold Condensed / Helvetica Neue LT Std 57 Condensed		6 point type
Bullets	Font Name: Helvetica Neue LT Std 55 Roman		5 point type
Bullets on same lines: end of statement separated from bulleted statement by two ems			Yes
Spacing of the hair lines from edge of box – i.e. Minimum of 2 spaces either side of Drug Fact Box			Yes
Tracking	0	Horizontal Scale:	97%-100%
Leading (Minimum space in body copy of Drug Facts)	6.5 pt.	Maximum Characters/Inch:	35
Barlines	1.5 pt.	Hairlines	0.50 pt.
Primary Display Panel Info			
Font size of Net Wt/Contents (Smallest character height in inches)			N/A
PDP dimensions (in square inches)			N/A
Font size of Statement of Identity (If not live text, to be measured in Helvetica capital "M")		V N/A	H N/A
Font size of Logo/Largest Copy on PDP (If not live text, to be measured in Helvetica capital "M")		V N/A	H N/A
Ratio of Statement of Identity to Logo/Largest Copy on PDP Statement of Identity (pt.) (Divided by) Largest Logo Copy (pt.)		V N/A	H N/A

Inside of card die-cut side



Outside of card, facing product (coated side)

GSK Regulatory Spec Box			Verified Date: 06.21.18
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Headings	Font Name: N/A		N/A
Subheadings	Font Name: N/A		N/A
Body text	Font Name: N/A		N/A
Bullets	Font Name: N/A		N/A
Bullets on same lines: end of statement separated from bulleted statement by two ems			N/A
Spacing of the hair lines from edge of box – i.e. Minimum of 2 spaces either side of Drug Fact Box			N/A
Tracking	N/A	Horizontal Scale:	N/A
Leading (Minimum space in body copy of Drug Facts)	N/A	Maximum Characters/Inch:	N/A
Barlines	N/A	Hairlines	N/A
Primary Display Panel Info			
Font size of Net Wt/Contents (Smallest character height in inches)			0.1624 in.
PDP dimensions (in square inches)			19.9 sq. in.
Font size of Statement of Identity (If not live text, to be measured in Helvetica capital "M")		V 13.3 pt.	H N/A
Font size of Logo/Largest Copy on PDP (If not live text, to be measured in Helvetica capital "M")		V 46.0 pt.	H N/A
Ratio of Statement of Identity to Logo/Largest Copy on PDP Statement of Identity (pt.) (Divided by) Largest Logo Copy (pt.)		V 28.9%	H N/A

Inside of card coated side

Sealing Area - No Print, No Varnish

Sealing Area

Drug Facts (continued)

- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat
- you have symptoms of an allergic reaction (such as difficulty breathing or rash)

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
- begin using the lozenge on your quit day
- **if you smoke your first cigarette within 30 minutes of waking up,** use 4 mg nicotine lozenge
- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2 mg 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. 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
- 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.**
- it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.

Other information

- store at 20 - 25°C (68 - 77°F)
- store in the original container

Inactive ingredients

acesulfame potassium, flavors, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, polysorbate 80, potassium aluminum silicate, sodium carbonate anhydrous, sucralose, titanium dioxide, xanthan gum

Questions or comments? call toll-free 1-xxx-xxx-xxxx

17-049CHFS

Outside of card, facing product (coated side)

Flip open for Directions and additional information

- **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: The lozenge containers are protected in a clear plastic shell, sealed to a printed card. Do not use if the printed card or plastic shell is torn or broken, or if there is any evidence that the printed card was separated from the plastic shell.

Retain this package for complete product information.

Drug Facts

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

Nicotine polacrilex, 2 mg.....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.

Ask a doctor before use if you have

- 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
- history of seizures

Ask a doctor or pharmacist before use if you are

- using a non-nicotine stop smoking drug
- taking a 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

Lot:

Exp:

0 0000-0000-00 0

EAS TAGGED

GSK Regulatory Spec Box — Verified Date: 09.28.17

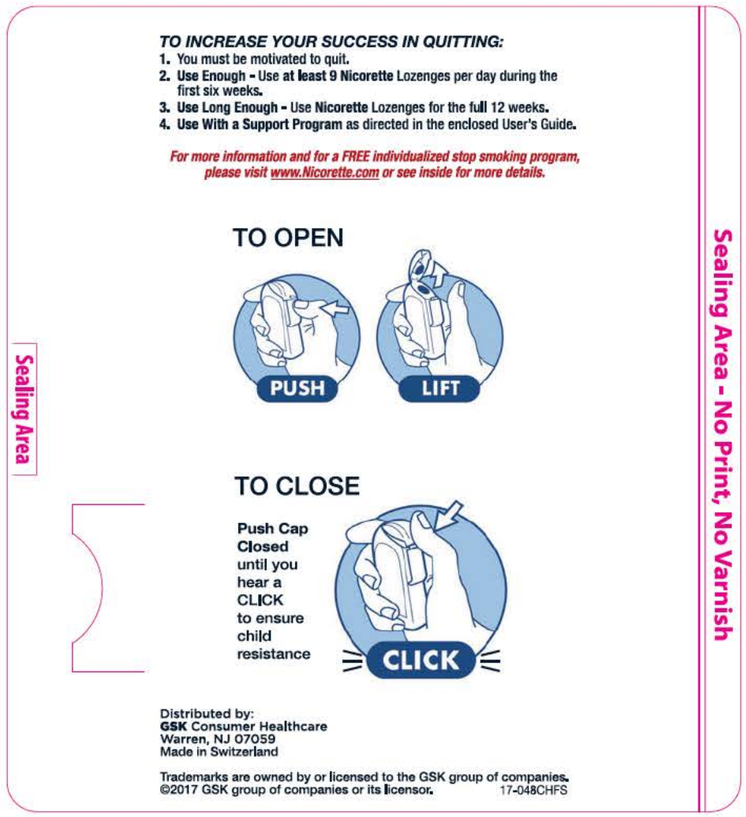
Drug Facts Info

Drug Facts (Title)	Font Name: Helvetica Neue LT Std 77 Bold Condensed Oblique		10 point type
Drug Facts (continued)	Font Name: Helvetica Neue LT Std 77 Bold Condensed Oblique/ Helvetica Neue LT Std 57 Condensed		8 point type
Headings	Font Name: Helvetica Neue LT Std 77 Bold Condensed Oblique		8 point type
Subheading	Font Name: Helvetica Neue LT Std 77 Bold Condensed		6 point type
Body text	Font Name: Helvetica Neue LT Std 77 Bold Condensed / Helvetica Neue LT Std 57 Condensed		6 point type
Bullets	Font Name: Helvetica Neue LT Std 55 Roman		5 point type
Bullets on same lines: end of statement separated from bulleted statement by two ems			Yes
Spacing of the hair lines from edge of box – i.e. Minimum of 2 spaces either side of Drug Fact Box			Yes
Tracking	0	Horizontal Scale:	97%-100%
Leading (Minimum space in body copy of Drug Facts)	6.5 pt.	Maximum Characters/Inch:	35
Barlines	1.5 pt.	Hairlines	0.50 pt.

Primary Display Panel Info

Font size of Net Wt/Contents (Smallest character height in inches)	N/A
PDP dimensions (in square inches)	N/A
Font size of Statement of Identity (If not live text, to be measured in Helvetica capital "M")	V N/A H N/A
Font size of Logo/Largest Copy on PDP (If not live text, to be measured in Helvetica capital "M")	V N/A H N/A
Ratio of Statement of Identity to Logo/Largest Copy on PDP Statement of Identity (pt.) (Divided by) Largest Logo Copy (pt.)	V N/A H N/A

Inside of card die-cut side



Outside of card, facing product (coated side)

GSK Regulatory Spec Box			Verified Date: 06.21.18
Drug Facts Info			
Drug Facts (Title)	Font Name: N/A		N/A
Drug Facts (continued)	Font Name: N/A		N/A
Headings	Font Name: N/A		N/A
Subheadings	Font Name: N/A		N/A
Body text	Font Name: N/A		N/A
Bullets	Font Name: N/A		N/A
Bullets on same lines: end of statement separated from bulleted statement by two ems			N/A
Spacing of the hair lines from edge of box – i.e. Minimum of 2 spaces either side of Drug Fact Box			N/A
Tracking	N/A	Horizontal Scale:	N/A
Leading (Minimum space in body copy of Drug Facts)	N/A	Maximum Characters/Inch:	N/A
Barlines	N/A	Hairlines	N/A
Primary Display Panel Info			
Font size of Net Wt/Contents (Smallest character height in inches)			0.1281 in.
PDP dimensions (in square inches)			25.74 sq. in.
Font size of Statement of Identity (If not live text, to be measured in Helvetica capital "M")		V 13.43pt.	N/A
Font size of Logo/Largest Copy on PDP (If not live text, to be measured in Helvetica capital "M")		V 46.4 pt.	N/A
Ratio of Statement of Identity to Logo/Largest Copy on PDP Statement of Identity (pt.) (Divided by) Largest Logo Copy (pt.)		V 28.9%	N/A

Inside of card coated side

Sealing Area - No Print, No Varnish

Sealing Area

Drug Facts (continued)

- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat
- you have symptoms of an allergic reaction (such as difficulty breathing or rash)

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
- begin using the lozenge on your quit day
- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2 mg nicotine lozenge
- **if you smoke your first cigarette within 30 minutes of waking up,** use 4 mg 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. 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
- 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.**
- it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.

Other information

- store at 20 - 25°C (68 - 77°F)
- store in the original container

Inactive ingredients

acesulfame potassium, flavors, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, polysorbate 80, potassium aluminum silicate, sodium carbonate anhydrous, sucralose, titanium dioxide, xanthan gum

Questions or comments? call toll-free 1-xxx-xxx-xxxx

17-051CHFS

Outside of card, facing product (coated side)

Flip open for Directions and additional information

- **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: The lozenge containers are protected in a clear plastic shell, sealed to a printed card. Do not use if the printed card or plastic shell is torn or broken, or if there is any evidence that the printed card was separated from the plastic shell.

Retain this package for complete product information.

Drug Facts

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

Nicotine polacrilex, 4 mg ..... 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.

Ask a doctor before use if you have

- 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
- history of seizures

Ask a doctor or pharmacist before use if you are

- using a non-nicotine stop smoking drug
- taking a 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

Lot:

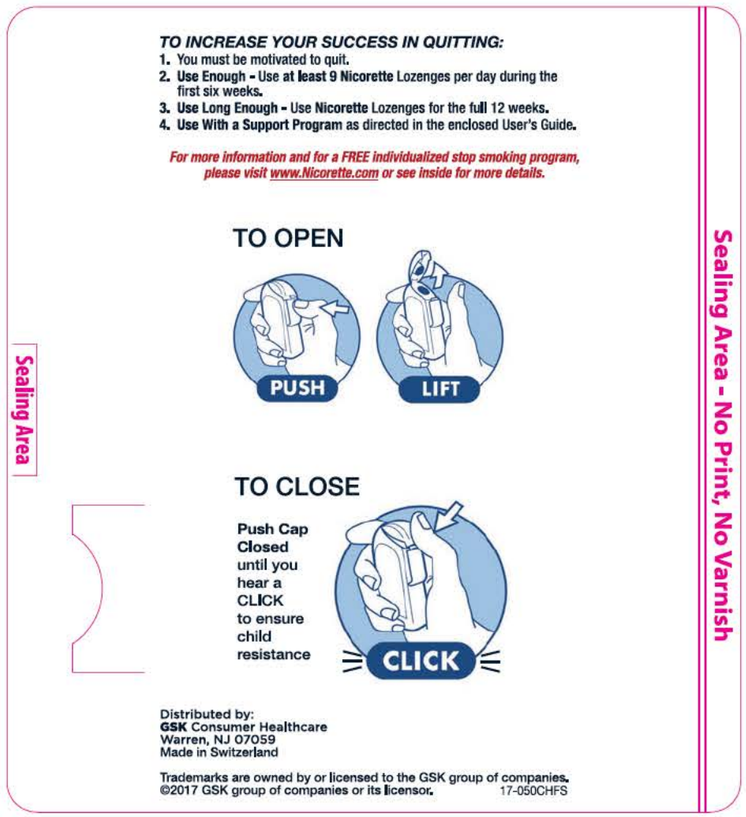
Exp:

0 0000-0000-00 0

EAS TAGGED

GSK Regulatory Spec Box			Verified Date: 09.28.17
Drug Facts Info			
Drug Facts (Title)	Font Name: Helvetica Neue LT Std 77 Bold Condensed Oblique		10 point type
Drug Facts (continued)	Font Name: Helvetica Neue LT Std 77 Bold Condensed Oblique/ Helvetica Neue LT Std 57 Condensed		8 point type
Headings	Font Name: Helvetica Neue LT Std 77 Bold Condensed Oblique		8 point type
Subheading	Font Name: Helvetica Neue LT Std 77 Bold Condensed		6 point type
Body text	Font Name: Helvetica Neue LT Std 77 Bold Condensed / Helvetica Neue LT Std 57 Condensed		6 point type
Bullets	Font Name: Helvetica Neue LT Std 55 Roman		5 point type
Bullets on same lines: end of statement separated from bulleted statement by two ems			Yes
Spacing of the hair lines from edge of box – i.e. Minimum of 2 spaces either side of Drug Fact Box			Yes
Tracking	0	Horizontal Scale:	97%-100%
Leading (Minimum space in body copy of Drug Facts)	6.5 pt.	Maximum Characters/Inch:	35
Barlines	1.5 pt.	Hairlines	0.50 pt.
Primary Display Panel Info			
Font size of Net Wt/Contents (Smallest character height in inches)			N/A
PDP dimensions (in square inches)			N/A
Font size of Statement of Identity (If not live text, to be measured in Helvetica capital "M")		V N/A	H N/A
Font size of Logo/Largest Copy on PDP (If not live text, to be measured in Helvetica capital "M")		V N/A	H N/A
Ratio of Statement of Identity to Logo/Largest Copy on PDP Statement of Identity (pt.) (Divided by) Largest Logo Copy (pt.)		V N/A	H N/A

Inside of card die-cut side



Outside of card, facing product (coated side)

GSK Regulatory Spec Box			Verified Date: 06.21.18
Drug Facts Info			
Drug Facts (Title)	Font Name: N/A		N/A
Drug Facts (continued)	Font Name: N/A		N/A
Headings	Font Name: N/A		N/A
Subheadings	Font Name: N/A		N/A
Body text	Font Name: N/A		N/A
Bullets	Font Name: N/A		N/A
Bullets on same lines: end of statement separated from bulleted statement by two ems			N/A
Spacing of the hair lines from edge of box – i.e. Minimum of 2 spaces either side of Drug Fact Box			N/A
Tracking	N/A	Horizontal Scale:	N/A
Leading (Minimum space in body copy of Drug Facts)	N/A	Maximum Characters/Inch:	N/A
Barlines	N/A	Hairlines	N/A
Primary Display Panel Info			
Font size of Net Wt/Contents (Smallest character height in inches)			0.1281 in.
PDP dimensions (in square inches)			25.74 sq. in.
Font size of Statement of Identity (If not live text, to be measured in Helvetica capital "M")		V 13.43pt.	N/A
Font size of Logo/Largest Copy on PDP (If not live text, to be measured in Helvetica capital "M")		V 46.4 pt.	N/A
Ratio of Statement of Identity to Logo/Largest Copy on PDP Statement of Identity (pt.) (Divided by) Largest Logo Copy (pt.)		V 28.9%	N/A

FRONT CARD

NDC 00000-000-00

gsk

Nicorette

nicotine polacrilex lozenge, 2 mg
stop smoking aid

Lozenge

Coated
Ice Mint

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 4 mg Lozenge.

120 LOZENGES, 2 mg EACH
(6-20 Lozenge Packs)

Includes User's Guide

← Data Matrix 000000XX 5mm

BACK CARD

TO INCREASE YOUR SUCCESS IN QUITTING:

1. You must be motivated to quit.
2. **Use Enough** • Use **at least 9 Nicorette** Lozenges per day during the first six weeks.
3. **Use Long Enough** • Use **Nicorette** Lozenges 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.

- **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: The lozenge containers are protected in a clear plastic **shell**, sealed to a printed card. Do not use if the printed card or plastic **shell** is torn or broken, or if there is any evidence that the printed card was separated from the plastic shell.

Retain this package for complete product information.

Drug Facts

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

Ask a doctor before use if you have
• 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
• history of seizures

Ask a doctor or pharmacist before use if you are
• using a non-nicotine stop smoking drug
• taking a 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
• you have symptoms of an allergic reaction (such as difficulty breathing or rash)

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
• begin using the lozenge on your quit day
• **if you smoke your first cigarette within 30 minutes of waking up,** use 4 mg nicotine lozenge
• **if you smoke your first cigarette more than 30 minutes after waking up,** use 2 mg 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. 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
• 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.**
• it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.

Other information
• store at 20 – 25°C (68 – 77°F)
• store in the original container

Inactive ingredients
acesulfame potassium, flavors, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, polysorbate 80, potassium aluminum silicate, sodium carbonate anhydrous, sucralose, titanium dioxide, xanthan gum

Questions or comments? call toll-free 1-xxx-xxx-xxxx

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Distributed by:
GSK Consumer Healthcare
Warren, NJ 07059
Made in Switzerland

17-052CHFS

0 0000-0000-00 0

TO OPEN

TO CLOSE

Push Cap Closed until you hear a CLICK to ensure child resistance

00000000

Lot
Exp:

EAS TAGGED

← Data Matrix 000000XX 5mm

GSK Regulatory Spec Box — Verified Date: 6.21.18

Drug Facts Info		
Drug Facts (Title)	Font Name: Helvetica Neue 77 Bold Condensed Oblique	11 point type
Drug Facts (continued)	Font Name: Helvetica Neue 77 Bold Condensed Oblique/Helvetica Neue 57 Condensed	N/A
Headings	Font Name: Helvetica Neue 77 Bold Condensed Oblique	9 point type
Subheadings	Font Name: Helvetica Neue 77 Bold Condensed	7 point type
Body text	Font Name: Helvetica Neue 57 Condensed/Helvetica Neue 77 Bold Condensed	7 point type
Bullets	Font Name: Helvetica Neue 55 Roman	5 point type
Bullets on same lines: end of statement separated from bulleted statement by two ems		N/A
Spacing of the hair lines from edge of box – i.e. Minimum of 2 spaces either side of Drug Fact Box		Yes

Tracking	0	Horizontal Scale:	100%
Leading (Minimum space in body copy of Drug Facts)	7.6 pt.	Maximum Characters/Inch:	37
Barlines	1.5 pt.	Hairlines	0.50 pt.

Primary Display Panel Info		
Font size of Net Wt/Contents (Smallest character height in inches)		0.189 in.
PDP dimensions (in square inches)		77 sq. in.
Font size of Statement of Identity (If not live text, to be measured in Helvetica capital "M")	V 24.51 pt	H N/A
Font size of Logo/Largest Copy on PDP (If not live text, to be measured in Helvetica capital "M")	V 85.5 pt	H N/A
Ratio of Statement of Identity to Logo/Largest Copy on PDP Statement of Identity (pt.) (Divided by) Largest Logo Copy (pt.)	V 28.7%	H N/A

FRONT CARD

Data Matrix
000000XX
5mm

BACK CARD

TO INCREASE YOUR SUCCESS IN QUITTING:

1. You must be motivated to quit.
2. **Use Enough** - Use **at least 9 Nicorette** Lozenges per day during the first six weeks.
3. **Use Long Enough** - Use **Nicorette** Lozenges 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.

- **not for sale to those under 18 years of age**
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Retain this package for complete product information.

Drug Facts

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

Ask a doctor before use if you have
- 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
- history of seizures

Ask a doctor or pharmacist before use if you are
- using a non-nicotine stop smoking drug
- taking a 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
- you have symptoms of an allergic reaction (such as difficulty breathing or rash)

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
- begin using the lozenge on your quit day
- **If you smoke your first cigarette more than 30 minutes after waking up,** use 2 mg nicotine lozenge
- **If you smoke your first cigarette within 30 minutes of waking up,** use 4 mg 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. 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
- 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.**
- it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.

Other information
- store at 20 – 25°C (68 – 77°F)
- store in the original container

Inactive ingredients
acesulfame potassium, flavors, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, polysorbate 80, potassium aluminum silicate, sodium carbonate anhydrous, sucralose, titanium dioxide, xanthan gum

Questions or comments? call toll-free 1-xxx-xxx-xxxx

Distributed by:
GSK Consumer Healthcare
Warren, NJ 07059
Made in Switzerland

17-053CHFS

0 0000-0000-00 0

EAS TAGGED

TO OPEN

TO CLOSE

Push Cap Closed until you hear a **CLICK** to ensure child resistance

00000000

Lot
Exp:

Data Matrix
000000XX
5mm

GSK Regulatory Spec Box — Verified Date: 6.21.18

Drug Facts Info			
Drug Facts (Title)	Font Name: Helvetica Neue 77 Bold Condensed Oblique		11 point type
Drug Facts (continued)	Font Name: Helvetica Neue 77 Bold Condensed Oblique/Helvetica Neue 57 Condensed		N/A
Headings	Font Name: Helvetica Neue 77 Bold Condensed Oblique		9 point type
Subheadings	Font Name: Helvetica Neue 77 Bold Condensed		7 point type
Body text	Font Name: Helvetica Neue 57 Condensed/Helvetica Neue 77 Bold Condensed		7 point type
Bullets	Font Name: Helvetica Neue 55 Roman		5 point type
Bullets on same lines: end of statement separated from bulleted statement by two ems			N/A
Spacing of the hair lines from edge of box – i.e. Minimum of 2 spaces either side of Drug Fact Box			Yes
Tracking	0	Horizontal Scale:	100%
Leading (Minimum space in body copy of Drug Facts)	7.6 pt.	Maximum Characters/Inch:	37
Barlines	1.5 pt.	Hairlines	0.50 pt.

Primary Display Panel Info			
Font size of Net Wt/Contents (Smallest character height in inches)			0.189 in.
PDP dimensions (in square inches)			77 sq. in.
Font size of Statement of Identity (If not live text, to be measured in Helvetica capital "M")	V 24.51 pt	H	N/A
Font size of Logo/Largest Copy on PDP (If not live text, to be measured in Helvetica capital "M")	V 85.5 pt	H	N/A
Ratio of Statement of Identity to Logo/Largest Copy on PDP Statement of Identity (pt.) (Divided by) Largest Logo Copy (pt.)	V 28.7%	H	N/A

PLACE THESE REMINDERS ON YOUR CALENDAR:

FRONT PANEL WHEN FOLDED

K/O PHARMACODE

BACK PANEL WHEN FOLDED

How to Use Nicorette Lozenges and Tips to Help You Quit Smoking.

Nicorette

nicotine polacrilex lozenge
2 mg and 4 mg User's Guide

Lozenge

PLANNING YOUR SUCCESS

1) The key to accomplishing anything important is commitment. When it comes to quitting smoking, that is especially true. **Nicorette** Lozenges can help if you really want to quit. **Nicorette** Lozenges help reduce withdrawal symptoms including nicotine craving associated with quitting smoking.
2) Your chances of staying off cigarettes are much better if you start with at least 9 **Nicorette** Lozenges daily. For best results, use the lozenges on a regular schedule (as outlined in this User's Guide).
3) Start using **Nicorette** Lozenges on your quit date.
4) This User's Guide outlines a 12-week plan for **Nicorette** Lozenges. Even though you may feel confident about your non-smoking status after a few weeks, it's important to stick with the plan to help you remain smoke free. Even a single cigarette can put you right back to square one.
5) **Nicorette** Lozenges work best when used together with a support plan. See information to the right for the MyQuit behavioral support program.
6) After the first six weeks, start using fewer **Nicorette** Lozenges, as directed in the instructions, gradually reducing your use over the next six weeks. If you feel the need to use the lozenges for a longer period to keep from smoking, talk to your health care provider.
7) If you have questions about using **Nicorette** Lozenges, call toll-free **1-XXX-XXX-XXXX**, or talk to your pharmacist or family doctor.

YES! YOU WANT TO QUIT.

Wonderful. You've made the most important decision of all, to stop smoking. And by choosing **Nicorette** Lozenges to help you, you're starting on the right path. Now remember, using **Nicorette** Lozenge doesn't just mean taking a **Nicorette** Lozenge. It means setting and following a program like the one we suggest in this User's Guide.

Your own success depends on your effort, your level of addiction to tobacco, and your commitment to following your program.

LET'S FACE IT.

Quitting smoking isn't easy! You or someone you know may have tried unsuccessfully. That's okay. It's hard to stop smoking the first time you try. The important part is to learn from your previous attempts, consider what went wrong and keep trying to quit until you succeed. Look to this User's Guide for support as you undergo this terrific task. The guide includes important information on how to use **Nicorette** Lozenges and also gives you tips to help you stop smoking. Refer back to it often for advice, answers, and encouragement to help you stay on track.

GET MOTIVATED. STAY MOTIVATED.

Everyone has a reason for quitting — whether you're concerned about your health, your appearance, family or peer pressure, or the effect of secondhand smoke on your loved ones — all of the above, or something else entirely. Whatever your reasons, write them down. There's a wallet card on the bottom right of this User's Guide. Write your reasons on the card and carry it with you. When you have an urge to smoke or experience a difficult moment it can help you focus on your reasons for quitting. Lots of people quit with a co-worker, spouse or friend and use them as a quitting buddy. You can help each other out by providing extra encouragement in tough moments.

There may be support groups in your area for people trying to quit. Call your local chapter of the American Lung Association, American Cancer Society or American Heart Association for further information. Toll-free phone numbers are printed on the back of the wallet card on the bottom right of this User's Guide.

UNDERSTANDING THE DOUBLE-EDGED SWORD.

Smoking has two addictive components, a physical and a mental need for the nicotine in tobacco. You need to conquer both to succeed. **Nicorette** Lozenges can ease your physical nicotine addiction. But your readiness and resolve are necessary to help overcome the mental side of your cigarette dependence. So once you're ready, it's time to begin. But first, read and consider the following important warnings.

IMPORTANT WARNINGS

This product is only for those who want to stop smoking. **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.

Ask a doctor before use if you have
- 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
- history of seizures

Ask a doctor or pharmacist before use if you are
- using a non-nicotine stop smoking drug
- taking a 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
- you have symptoms of an allergic reaction (such as difficulty breathing or rash)

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.

YOU'RE READY TO START.

Okay, you're ready. To become a non-smoker, start today. Now before you do anything else, you have a bit of planning to do. Read this User's Guide all the way through. You want to make sure you bought the right dose to start. If you typically smoke **your first cigarette within 30 minutes of waking up,** use the 4 mg **Nicorette** Lozenges. If you smoke **your first cigarette more than 30 minutes after waking up,** use the 2 mg **Nicorette** Lozenges. Next, plan your quitting schedule. Get a calendar to follow your progress and mark the following four important dates (see the reminders on the upper left side of this leaflet).

THE PROGRAM

STEP 1 (Weeks 1-6) Starting on your quit date it's best to use at least 9 Nicorette Lozenges each day, one every 1-2 hours. First choose the day you plan to quit (make it soon). Place the Step 1 reminder on this date. That's the day you will start using **Nicorette** Lozenges to calm your cravings for nicotine and help you stay smoke free. Prior to the quit date, get rid of all your cigarettes to remove temptations and make it more difficult to start smoking again.

Use a **Nicorette** Lozenge every 1 to 2 hours and at least 9 lozenges each day for the first 6 weeks to help prevent unexpected cravings and improve your chances of quitting. **These aren't ordinary lozenges**. Place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. **Do not chew or swallow the 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. **Remember to read the "USING Nicorette LOZENGES PROPERLY" section before you take your first Nicorette Lozenge**.

STEP 2 (The next three weeks, that is weeks 7-9).
At the beginning of week 7 start using fewer Nicorette Lozenges, one every 2-4 hours. After six weeks, you should wait a little longer between lozenges, one lozenge every two to four hours. This will help you gradually use fewer **Nicorette** Lozenges. Put the Step 2 reminder on the first day of week 7 to help remind you when to start reducing the number of Nicorette Lozenges you take.

STEP 3 (The last three weeks, that is weeks 10-12).
At the beginning of week 10, reduce Nicorette Lozenge use even further, one every 4-8 hours. At the beginning of week 10 further decrease the number of **Nicorette** Lozenges you use each day to reduce the amount of nicotine you get. You should do this by using one lozenge every 4 to 8 hours. Put the Step 3 reminder on the first day of week 10 so you know when you should be starting this last step to becoming smoke and nicotine-free.

END At the end of week 12 you'll complete Nicorette Lozenge therapy.
Put the "EX-SMOKER" reminder on your calendar on the date 12 weeks after the day you stopped smoking and started using **Nicorette** Lozenges.

BE PREPARED.

Since smoking is an addiction, it is hard to quit. Even after you stop, there will be times when you WANT a cigarette, sometimes strongly (see also section on "**CHALLENGES TO WATCH FOR**"). The best defense is to be prepared. Plan now for handling tough times so you don't give in. Think about situations where you usually get an urge to smoke or where you might experience strong urges to smoke (for example, spending time with smokers or drinking alcohol — try to avoid these situations if those things tempt you to smoke).

Change your habits. Take your coffee break somewhere else. Take a walk. Break the association between your usual habit and cigarettes.

If you do encounter a situation where you feel a strong urge to smoke, fight it! Take a break from the situation; keep yourself busy or distracted with other activities. Remind yourself why you want to quit, and that having "just one" will really hurt your goal of quitting!

Assemble a "survival package" — items that can keep you distracted in case you get an urge to smoke. For example, cinnamon gum or hard candy, relaxing music, things to keep your hands busy like a smooth stone or paper clips, etc.

Track your quit progress. Use a journal or the MyQuit app on your mobile phone to note if and when you get an urge to smoke. Note how many pieces of **Nicorette** Lozenges you use each day. If you slip and have a cigarette, don't give up. Stop smoking again and get back on your program with **Nicorette** Lozenges.

Establish your support network. Keep friends' and family members' phone numbers ready to get the moral support you need. Before quitting, ask friends and family to support and encourage you. Think of specific ways they can help.

Reward yourself. Set aside little gifts to encourage yourself which you can earn by overcoming difficult hurdles.

HOW Nicorette LOZENGES WORK.

Nicorette Lozenges are a form of Nicotine Replacement Therapy. They deliver nicotine to your body, temporarily relieving craving and nicotine withdrawal symptoms when you quit smoking. But unlike cigarettes, **Nicorette** Lozenges deliver a lower, steady level of nicotine to your blood. When used as directed, **Nicorette** Lozenges help you regulate, control, and gradually reduce your body's craving for nicotine.

The good news is that **Nicorette** Lozenges contain no tar or carbon monoxide, and therefore don't present the same medical risks as cigarettes.

However, the lozenges still deliver nicotine, the addictive ingredient in cigarettes. And for some people the nicotine in **Nicorette** Lozenges can occasionally cause mouth or throat irritation, headaches, nausea, hiccups, upset stomach or dizziness.

USING Nicorette LOZENGES PROPERLY.

Remember, **Nicorette Lozenges aren't like ordinary lozenges such as cough drops.** This lozenge is designed to deliver nicotine into your system through the lining of your mouth, not in your stomach like most other medicines. It is important to minimize swallowing the dissolved medicine in these lozenges so that it can be properly absorbed in your mouth.

WALLET CARD
My most important reasons to quit smoking are:

MyQuit
Program brought to you by

Nicorette
nicotine polacrilex lozenge
Lozenge
and GSK

Nicorette has created the **MyQuit** program to provide you with 360° support wherever and whenever you need it. The program provides a network of tools to help you get through those tough moments.

- **To Your Inbox:** Stay motivated with our personalized email support program that sends encouragement and tips straight to your inbox.
- **On The Web:** Get helpful advice, tips and inspiration from ex-smokers on Quit.com.
- **On The Go:** Log cravings and track your personal progress on your mobile phone with the MyQuit App.

To learn more visit www.quit.com

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Do not use more than one lozenge at a time, or many lozenges one after another since this can cause hiccups, heartburn, nausea or other side effects.

Read all the following instructions before using **Nicorette** Lozenges. Refer to them often to make sure you're using **Nicorette** Lozenges correctly.

IMPORTANT: Don't worry or give up if you do not like the taste of the lozenge at first. Nicorette Lozenges are a medication, not a candy. Most people get used to the taste after a day or two. Remember, staying with the plan will help you quit. Begin using Nicorette Lozenges on your quit date.

1) Remove the **Nicorette** Lozenge from the immediate container. Place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. **Do not chew or swallow the lozenge**. You may feel a warm or tingling sensation.
2) Occasionally move the lozenge from one side of your mouth to the other side until completely dissolved.

To reduce cravings or urges to smoke and other withdrawal symptoms, use **Nicorette** Lozenges according to the following dosage schedule:

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

Do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day. At the end of 12 weeks (3 months) you will have completed treatment.

FOR THE BEST CHANCE OF QUITTING, use **Nicorette** Lozenges on a regular schedule, using at least 9 lozenges a day during the first 6 weeks. That will help your body better adjust to the lack of cigarettes and better help prevent cravings. Some people may need more lozenges to reduce their cravings. Do not exceed the recommended maximum daily dosage of 20 lozenges per day. Do not continuously use one lozenge after another, since this may cause you hiccups, heartburn, nausea or other side effects.

Do not eat or drink 15 minutes before using or while the lozenge is in your mouth.

WALLET CARD

WHERE TO CALL FOR HELP:

American Lung Association
1-800-586-4872

American Cancer Society
1-800-227-2345

American Heart Association
1-800-242-8721

Quitting Buddy or Friend who has Quit

CUTTING BACK ON YOUR Nicorette LOZENGE USAGE.

The whole reason for using **Nicorette** Lozenges is to decrease and slowly eliminate your need for nicotine, while you control cravings. So, as the schedule to the left indicates, you should gradually reduce the amount of **Nicorette** Lozenges you take per day. Some people find it easier to reduce by substituting ordinary sweets or sugar free candy for some of the **Nicorette** Lozenges they would normally use. As time goes on, you can increase the number of pieces of candy as you further reduce your use of **Nicorette** Lozenges. **It is important to complete treatment.** If you still feel the need to use **Nicorette** Lozenges to keep from smoking after week 12, talk with your health care provider.

MAKE QUITTING EASIER ON YOURSELF.

Soon after your quit date, parties, bars, celebrations, and socializing may all tempt you to smoke. Please remember these tips to help you resist those urges and stay smoke-free.

The Day You Quit Smoking:

- Look to your family and friends for support. Let them know what to do or avoid doing to help you quit.
- Throw away ALL cigarettes, ashtrays, matches, lighters. You don't need them. You don't want them and you want to make it difficult to go back.
- Keep yourself occupied. Take a walk. See a movie. See friends. Do anything to keep your mind off cigarettes.
- Calculate all the money you'll save by not buying cigarettes. Probably well over $1,000 a year! $1,000 a year? Think of what you can spend it on!
- Know what situations are going to make you want to smoke. Plan now how you'll avoid them or deal with them so you don't smoke.
- Keep **Nicorette** Lozenges next to your bed so you're prepared when you get up. A lot of people get cravings first thing in the morning.
- Make an appointment to see your dentist and get the tobacco stains cleaned off. While you're getting rid of the evidence of cigarettes in the house, do the same for your teeth. Have clothes or drapes that smell of smoking cleaned.
- Now that your house is smoke-free, try to spend most of your time in smoke-free environments.
- If you usually smoked with coffee or alcohol, try to keep away from them for now. Remember you are also trying to break a habit.
- Smoking is a "hands-on" habit. So use something else to occupy your hands: a rubber band or a pen.
- Now's a good time to get active. Find activities to take your mind off cigarettes and relax. Take up jogging, swimming, or walking.
- Don't stress out about gaining weight. Dieting now may weaken your efforts to quit smoking. Eat sensibly and exercise daily; drink large quantities of water and fruit juices; this can help your chances of staying smoke-free.
- Laugh. Watch a sitcom. Read a comic book. It really helps.

REMEMBER: Urges to smoke are temporary. They'll pass, even if you don't smoke.

WHAT YOU CAN EXPECT.

As you are successful at staying smoke-free, initially you will probably notice a few of the following typical withdrawal symptoms, so don't be surprised. Use of **Nicorette** Lozenges reduces these symptoms, but may not eliminate them entirely. They will go away with time. Stay focused on your goal of becoming an ex-smoker. Research shows that if you manage to avoid all smoking in the first week (that means not having a single puff), your chances of success increase dramatically.

The First Few Days. You may feel nervous or irritable or have difficulty concentrating during the first few days after you quit smoking. Your body needs time to regain balance. Initially, you might feel a little out of sorts, get headaches, feel light-headed, or have trouble sleeping. Your smoker's cough may get worse before it improves. But fear not, it's a positive sign. Coughing helps clean your lungs of the tar residue you got from smoking.

After a Couple of Weeks. Your confidence and ability to cope with urges to smoke should be getting stronger. But don't be over-confident and think you can smoke just one cigarette. Even now, having even a single puff can lead to a return to smoking cigarettes regularly. Be prepared, and remember why you wanted to stop smoking. Have you noticed that your sense of taste and smell has improved? You are probably coughing less and finding it easier to breathe. You've also probably noticed your withdrawal symptoms are subsiding (though don't worry if they're still there: they last longer for some people). These are all positive signs that your body is getting used to your success at stopping smoking.

By The End of The First Month. You are less likely to have cravings for cigarettes as often. However sudden cravings may still happen, and when they do, be on your guard, as they can be strong and seem to come out of the blue. Be prepared for these challenging times. The key is do what you can so these unexpected cravings can't beat you. Keep focused on the ways non-smokers are more attractive than smokers. Their breath smells better. Their clothes and hair are fresher. Their teeth are cleaner and brighter. Their skin is less likely to wrinkle. Not smoking around children and your friends is also healthier for them too.

WHAT IF YOU DO SLIP AND SMOKE?

"What if I relapse?" One cigarette is a slip-up, but it's not the end of the quit effort. Everybody slips at something. The key is this: forgive yourself and stop at that one cigarette. Don't let this slip ruin your good intentions, keep at your quit attempt. So, throw out your cigarettes and continue with your quit attempt, keeping in mind what went wrong and led to the slip.

If you do go back to smoking, certainly don't throw out your **Nicorette** Lozenges. Keep them for the next time you're ready to quit. In fact research says that even if you are back to smoking regularly the best thing you can do is learn and try again.

Try to understand the reason you had those cigarettes that made you slip. That's important, because now you can plan better to deal with these moments next time. It's true you stumbled, but don't think of yourself as having failed. Encourage yourself by treating the last attempt as a learning experience, even a "trial run" for the real thing.

Take a look at the usage instructions and check that you used the **Nicorette** Lozenges correctly and for the full 12 weeks of the program. When you try again make sure you use enough and the right way. That way you'll be best equipped to deal with the unexpected cravings.

Don't forget; quitting isn't easy and it takes practice to do anything. Stopping smoking is no different.

YOU'VE MADE IT.

Once your twelve week quitting program is over, you've taken your last **Nicorette** Lozenge. Now you are both cigarette and nicotine-free. Get up and give yourself a standing ovation. We mean it. Do you realize that you have just done a really difficult thing?

Now's a good time to think back on the process. Think of all your reasons for quitting smoking. Think of your goals. Think of how they're going to be a reality now.

Think of what you're going to do with your newly liberated cigarette money. The places you can now go smoke-free. Think of the extra time you may have added to your life and what you can do with it. And although you may still experience the occasional temptation, and cigarettes still want you back, think positively. Think forward. And consider yourself a proud non-smoker.

FREQUENTLY ASKED QUESTIONS.

1. When I stop smoking and start using Nicorette Lozenges how will I feel?
Nicorette Lozenges help reduce cravings, but be prepared for some nicotine withdrawal symptoms. After you stop smoking they can begin almost at once and are normally at their strongest during the first three or four days. For some people, any of the following may occur:

- unexpected craving or urges for cigarettes
- anxiety, irritability, restlessness, mood changes, nervousness
- drowsiness
- trouble concentrating
- increased appetite and weight gain
- headaches, muscular pain, constipation, fatigue

Nicorette Lozenges are designed to reduce the craving for nicotine you used to satisfy with cigarettes. **Nicorette** Lozenges can also help provide relief from other withdrawal symptoms such as irritability and nervousness.

2. Are Nicorette Lozenges just swapping one type of nicotine addiction for another?
Nicorette Lozenges do contain nicotine, however there is probably less nicotine in your daily dose of lozenges than in your cigarettes. **Nicorette** Lozenges give you enough nicotine to help you combat the physical withdrawal symptoms so you can cope with the mental side of stopping smoking. Also, since the nicotine from the lozenges goes into your blood stream more slowly, it produces less of the effects of nicotine that people find rewarding. In fact, when used as directed in the 12 week program, **Nicorette** Lozenges gradually wean you off your dependence for both nicotine and cigarettes.

3. Can Nicorette Lozenges do any harm?
Some people with conditions like heart disease or people taking prescription medicine for asthma or depression should not use this product without talking to their doctor–check the **"IMPORTANT WARNINGS"** on the front of this leaflet. You may also experience side effects such as hiccups, mouth or throat irritation, heartburn or other stomach problems such as nausea especially if **Nicorette** Lozenges are chewed or swallowed. In any case, **Nicorette** Lozenges do not contain the tar, carbon monoxide, and other toxins present in cigarette smoke.

4. Will I put on weight?
In the first couple of months after quitting smoking, some people do put on a few pounds. But think of it this way. Overall, you'll be healthier and look better. You can always tackle your weight by changing your diet and increasing the amount you exercise once you have gotten through the difficult part of stopping smoking.

5. Does taking Nicorette Lozenges cost more than smoking?
If you normally smoke a pack and a half a day, your total cost of using **Nicorette** Lozenges during the 12-week period is about the same as smoking. But guess what? After you've finished the **Nicorette** Lozenge program all that money you used to spend on cigarettes is now savings. And think of the health issues you'll hopefully be able to avoid.

6. What if I have a cigarette and start smoking?
Don't panic. First, don't think badly of yourself. Throw away your cigarettes and forgive yourself. Then think about what went wrong and get back on track. In fact people who have already tried to stop smoking are more likely to be successful the next time.

CHALLENGES TO WATCH FOR.

Once you quit smoking, you are likely to experience periodic, and sometimes intense, temptations to smoke. Certain situations present special challenges. Some common ones include:

Stress and upset.
When you are feeling stressed or upset, you may think a cigarette will make everything better. It won't. Find other ways to relax and unwind.

The blues.
You may be especially vulnerable when you feel bored or blue. Remember that having a cigarette will just make you feel worse.

Smoking cues.
Seeing cigarettes or watching other people smoke can trigger temptation. Remember that you choose not to smoke anymore.

Alcohol.
Drinking and smoking seem to go together, and alcoholic beverages may weaken your resolve, making drinking dangerous to your quit effort. Avoid drinking early in your quit effort, and try to drink with non-smokers.

Automatic slips.
Sometimes you may find yourself preparing to smoke without even realizing it. Watch out for those moments when your hand seems to "automatically" reach for a cigarette.

Watch out for these situations: they can trigger a relapse. You probably know which one(s) are most dangerous for you; plan ahead to deal with the situation effectively. Always remember that you're trying to break a habit, and the most important thing is to do something to combat the urge in these situations.

COPING AFTER QUITTING.

The key to staying smoke-free is to prepare for and cope with challenges as they occur. If you find yourself tempted to smoke, do something! Here are some things to consider:

- Escape. Leave the situation, even for a few minutes. Most temptations don't last long.
- Distract yourself. Get your mind off smoking. Think of something else or get busy with something.
- Relax. Don't let stress get to you. Think of pleasant, relaxing things; breathe slowly and regularly. Let the stress drain out of you.
- Talk yourself out of it. What you say to yourself matters. So, remind yourself how important it is for you to quit; remind yourself you can't have just one; or just command yourself to STOP.

For more information please visit www.nicorette.com

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-330/S-21

CLINICAL REVIEW

Department of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Nonprescription Drug Products

Medical Officer's Memorandum

NDA:	**21330/S-021**
SDN:	**167**
Sponsor:	**GlaxoSmithKline Consumer Healthcare**
Drug:	**Nicorette Lozenges, 2mg and 4 mg**
Indication:	**Reduction of withdrawal symptoms, including nicotine craving associated with quitting smoking**
Date of Submission:	**February 22, 2018**
Date Received:	**February 22, 2018**
Date Completed:	**July 24, 2018**
Reviewer:	**Jenny Kelty, MD**

1 INTRODUCTION

This is the Division of Nonprescription Drug Products (DNDP) Medical Officer's clinical safety review of two pharmacokinetic studies submitted by GlaxoSmithKline Consumer Healthcare (GSK) in support of a Supplemental New Drug Application (sNDA) for a new formulation of Nicorette (nicotine polacrilex) lozenges, 2 mg and 4 mg. The proposed name for the new formulation is Nicorette Coated Ice Mint Lozenge. (b)(4)

The proposed lozenge is a coated, mint flavored lozenge and contains the same active ingredient (nicotine polacrilex) and the same strengths (2 mg and 4 mg) as the currently approved Nicorette original lozenges. The proposed lozenges were developed to be bioequivalent to the Nicorette original lozenges and have identical labeling and use instructions as the current Nicorette lozenges. The proposed lozenges have a different formulation, and are different in shape, size, and weight compared to the Nicorette original lozenges.

2 EXECUTIVE SUMMARY

The sponsor submitted two pharmacokinetic studies to support its supplemental NDA for a new formulation of Nicorette Lozenge – Nicorette Coated Ice Mint Lozenge. The adverse events from the pooled safety data from the two studies showed that the largest discrepancies between the

proposed product and NiQuitin 4 mg were nausea, hiccups, throat irritation, and dyspepsia – more subjects experienced these with the proposed Nicorette Coated Ice Mint Lozenge. However, these adverse events are already known to occur with NRT use and do not indicate any new safety signals for the proposed product. Also, these known adverse events are adequately addressed in the proposed labeling which is consistent with the current Drug Facts label (DFL) for Nicorette lozenges.

The proposed newly formulated product has a similar appearance to a tablet. The similarity in appearance to a tablet may be confusing to consumers and lead to swallowing of the tablet rather than dissolving it in the mouth. Ingestion of the tablet may result in delay or reduction in absorption leading to reduced efficacy but is not a safety issue. Further, the labeling of the proposed product adequately identifies the product as a lozenge and informs consumers that it should not be chewed or swallowed.

3 REVIEW OF PHARMACOKINETIC STUDIES FOR CLINICAL SAFETY

3.1 STUDY CO-160518135743-SCCT

Study Title:
A Single-Dose, Two-Period Crossover, Randomized, Fasting, Open-Label, Bioequivalence Study Between Two Commercially Available NRT Products in Adult Healthy Smokers

Primary Objective:
To demonstrate bioequivalence between Nicorette Peppermint lozenge 4 mg (reference product) and Nicorette Mint Lozenge 4 mg (test product)

Secondary Objectives:

- To further describe the nicotine single-dose pharmacokinetics of the investigational products
- To assess the time until complete dissolution of each treatment's lozenge in the mouth
- To evaluate the tolerability of the treatments in terms of spontaneously reported and observed Adverse Events (AEs)

This study was a single-dose, open-label, randomized, crossover study comparing the pharmacokinetic properties of the proposed 4 mg Nicorette Coated Ice Mint Lozenge versus 4 mg Nicorette Original Lozenge under fasted conditions in 227 healthy adult male and female volunteer smokers.

The study was conducted in two study sites in Sweden. Subjects were asked to abstain from both smoking and the use of other nicotine products before and during the assessment periods. All

subjects abstained from nicotine for 12 hours before receiving the study drug. All subjects fasted for 10 hours overnight before receiving study drug. All subjects continued to fast and refrained from lying down during the first 4 hours after dosing.

Blood for pharmacokinetic analyses was drawn pre-dose (i.e. within 5 minutes before drug administration) and at 3, 5, 10, 15, 20, 30, 40, 50, and 60 minutes, as well as, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after start of drug administration. Thus, 18 samples were collected per treatment visit. Registration of dissolution time was done. Subjects were monitored throughout the study period to capture any AEs that did occur. The mean dissolution time of the proposed product was 19.8 minutes (SD 11.39, range 5-107 minutes)

Healthy men and women between the ages of 19 and 55 years, inclusive, were enrolled. The subjects had to have a Body Mass Index (BMI) between 18.5 and 30 kg/m^2. Subjects were to be smokers of at least 10 cigarettes per day and were to have do so for at least one year preceding inclusion. Women were required to be in a postmenopausal state or in a premenopausal/perimenopausal state with an effective means of contraception. Men had to have no pregnant or lactating spouse or partner at screening and willingness to utilize an acceptable form of birth control with spouse or any potential partner during the study and for 30 days thereafter.

The following clinical laboratory tests were conducted at screening: hemoglobin, aspartate transaminase, alanine transaminase, alkaline phosphatase, Hepatitis B, Hepatitis C, HIV, HCG, FSH. Clinical laboratory tests from the screening visit were clinically normal, as judged by the investigator, in order for a subject to be eligible for enrollment. Blood pressure and pulse rate were measured at screening. Also, a 12-lead ECG was obtained at the screening visit. There were no abnormal laboratory values or procedures during the study.

Two-hundred thirty (230) subjects were planned and 227 subjects, 100 males and 127 females, were randomized to treatment. And 218 subjects completed both treatments of the study and 219 received both doses, but one subject withdrew from the study after the second treatment administration. All subjects that received any treatment were included in the safety analysis. In total, 9 subjects discontinued after randomization:

- 8 subjects discontinued prior to the second treatment visit, but after completing the first treatment.
- 1 subject withdrew during the second treatment visit “due to personal reasons”
- No subject discontinued from the study due to an AE.

Safety Results

In total, 314 treatment-emergent AEs were reported. Two-hundred thirty-four (234) of these were considered possibly, probably or very likely related to treatment. Of the 234 AEs, 203 were considered mild in severity, 28 were moderate, and 3 were severe. The 3 severe AEs were 2

nausea and 1 vomiting. Two severe events (one nausea and one vomiting) occurred in the Nicorette Mint Original Lozenge (NML) 4 mg arm. There was one severe event (nausea) in the Nicorette Peppermint Lozenge (NPL, proposed lozenge) 4 mg arm. There were no deaths or pregnancies reported in this study.

One non-treatment related SAE was reported in this study. Subject ID (b)(6) experienced a spontaneous pneumothorax and was hospitalized during the period between the two treatment visits, but recovered prior to the second treatment. No deaths, pregnancies or other significant AEs were reported.

Sixty-four (64) subjects experienced at least one AE possibly, probably or very likely related to treatment with NML 4 mg. The corresponding numbers with NPL 4 mg was 81.

Gastrointestinal Disorders represented the most commonly reported AEs, followed by Respiratory and Thoracic Disorders. The most common AEs were nausea, throat irritation, and headache. In general, AEs were consistent with the current understanding of the safety profile for nicotine lozenges. Table 2 presents the numbers of subjects who had the most common AEs by Preferred Term.

Table 1: Summary of Subjects with the Most Common AEs

Adverse Event (Preferred Term)	**NPL 4 mg* (n=221)**	**NML 4 mg* (n=225)**
Nausea	36	24
Throat Irritation	25	20
Headache	12	11
Dyspepsia	11	8
Hiccups	13	5
Vertigo	9	8

Source: Adapted from Sponsor's Table 14, Full Clinical Study Report for Study CO-160518135743-SCCT, pg. 45.
*NPL 4 mg=Nicorette Peppermint Lozenge (proposed product); NML 4 mg=Nicorette Mint Original/Mint Lozenge (reference product)

Reviewer Comment

Overall, the AE data do not indicate any new clinical safety issues with the proposed new formulation in this study.

3.2 STUDY NICTDP1076

Study Title:

Comparative Pharmacokinetic Study of New Oral Nicotine Replacement Therapy Products – A Study in Healthy Smokers

Primary Objective:

Demonstrate bioequivalence between NSL2L and NiQuitin lozenge 2 mg, and between NSL4M and NiQuitin lozenge 4 mg.

Secondary objectives:

- To describe the single-dose pharmacokinetics of NSL4L and NSL4H. The parameters described were cC_{max}, $cAUC_t$ and $cAUC_\infty$

- To evaluate the time at which the maximum concentration was observed (t_{max}), the terminal elimination rate constant (λ_z) and the terminal half-life ($t_{1/2}$) for the NSL (b)(4) and NiQuitin lozenge

- To evaluate the tolerability and safety

- To describe the time course of urges to smoke

- To evaluate the palatability

- To evaluate irritation in mouth and throat

- To evaluate the time until complete tablet dissolution in the mouth

This is a single-dose, open-label, randomized, 5-period crossover study comparing the pharmacokinetic properties of both the 2 mg and 4 mg Nicorette Coated Ice Mint Lozenges versus 2 mg and 4 mg NiQuitin lozenges (European marketed brand of Nicorette and identical to the Nicorette Original Lozenge in the United States) under fed conditions. As a secondary objective, this study also evaluated (b)(4) (4 mg lozenge with a low level of buffer capacity and 4 mg lozenge with a high level of buffer capacity) to gain a better understanding of the effects of buffer level on pharmacokinetic and pharmacodynamic parameters. The study was conducted in two study sites in Sweden. The study was conducted in healthy male and female volunteer smokers who were asked to abstain from both smoking and the use of other nicotine products before and during the assessment periods. All subjects abstained from nicotine for 12 hours before receiving the study drug. Subjects were monitored to capture any adverse events that occurred.

At treatment visits, blood samples for pharmacokinetic analyses (of nicotine in plasma) were drawn before and at 7.5, 15, 20, 30, 40, 50, and 60 minutes, as well as at 1.25, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after start of drug administration. Urges to smoke were rated (using a Likert scale with four ordered categories) before and at 2, 5, 10, 15, 20, 25, 30, 45, and 60 minutes after start of administration. No subjects with clinically relevant abnormal laboratory results were included in this study.

The following clinical laboratory tests were conducted at screening: hemoglobin, aspartate transaminase, alanine transaminase, alkaline phosphatase, Hepatitis B, Hepatitis C, HIV, HCG, FSH. Clinical laboratory tests from the screening visit were clinically normal, as judged by the investigator, for a subject to be eligible for enrollment. Blood pressure and pulse rate were measured at screening. Also, a 12-lead ECG was obtained at the screening visit. There were no abnormal laboratory values or procedures during the study.

Palatability was measured with a 100 mm visual analogue scale (VAS) immediately after dissolution of the product.

Irritation in mouth/throat was measured with a 100 mm VAS before and at 5 minutes after start of administration, as well as immediately after dissolution of the product.

The time until complete tablet dissolution was recorded.

One-hundred (100) subjects received five single doses of the investigational products (NSL2L, NiQuitin lozenge 2 mg, NSL4M (same as proposed 4 mg product), NiQuitin lozenge 4 mg and either of NSL4L or NSL4H) on separate treatment visits. Four subjects did not receive all doses (two subjects due to pregnancy, one subject was withdrawn due to poor compliance, and one subject discontinued because he/she was no longer willing to participate due to traveling). Periods of at least 36 hours separated the treatment visits.

Palatability

Palatability measurements were also obtained during this study, but no statistical tests for differences were performed. Palatability measurements were similar between the proposed product and the reference product.

Irritation in Mouth and Throat

The following table presents the across-subject means and standard deviations for mouth and throat irritation for the 4 mg products.

Table 2 Irritation in Mouth and Throat for the 4 mg Products (mm, Mean (SD))

Treatment *	n	Prior to treatment	5 min	After dissolution
NSL4L	46	3 (9)	43 (23)	35 (27)
NSL4M	97	3 (9)	31 (25)	27 (24)
NSL4H	50	1 (4)	44 (30)	34 (27)
NiQuitin™ lozenge 4 mg	99	2 (8)	26 (23)	21 (21)

Source: Sponsor's Table 17 (Clinical Study Report NICTDP1076, pg. 45)

*NSL4L=Nicorette Strongmint 4 mg Lozenge low buffer capacity; NSL4M=Nicorette Strongmint 4 mg (proposed product); NSL4H=Nicorette Strongmint 4 mg high buffer capacity; NiQuitin lozenge 4 mg is the reference product (same as Nicorette Original/Mint Lozenge).

Reviewer Comment

According to the above table, subjective mouth irritation scores were higher for NSL4M (study drug) than for NiQuitin lozenge (reference product). Mouth irritation can occur with nicotine lozenges and the clinical significance of the differences between the scores is not known.

Adverse Events

The safety analysis dataset included all subjects who received at least one dose of study medication (n=100 subjects). Table 3 below summarizes the number of AEs and subjects who reported them per arm.

Table 3: Number of Treatment-Related AEs and Number of Subjects

Treatment	AEs	Subjects
NSL2L	14	12
NSL4L	16	12
NSL4M	31	23
NSL4H	12	9
NiQuitin 2 mg	10	7
NiQuitin 4m g	14	12

Reviewer's Comment

NSL4M (proposed product) had the highest number of AEs reported in the study.

There were no deaths, or other SAEs in this study. The sponsor reports a total of 182 treatment-emergent AEs were reported. Ninety-seven (97) of these AEs were judged to be possibly treatment-related. One (1) of the AEs was categorized as severe, 38 were moderate and 58 were of mild intensity. Table 3 below presents the most common adverse events reported by subjects that occurred in the NSL4M arm compared to the NiQuitin 4 mg arm. The body system most affected by AEs was the gastrointestinal tract, with nausea as the most frequently reported. There were no indications that the types of AEs of the NSL (b)(4) differ from those of other oral nicotine replacement products.

Table 4: Summary of Subjects with the Most Common AEs for NSL4M (proposed product) and NiQuitin 4 mg Lozenge

Adverse Event (Preferred Term)	NSL4M (n=103)	NiQuitin 4 mg (n=104)
Nausea	9	4
Cough	4	0
Throat tightness	3	1

Headache	3	1
Dyspepsia	3	0

Source: Adapted from Sponsor's Table 18, Full Clinical Study Report for Study NICTCP1076, pg. 46.

Reviewer Comment:

There was one event of nausea that was categorized as severe in the NSL4M arm, one event of joint dislocation that was categorized as severe in the NSL 2 mg arm. There was one event of headache that was categorized as severe in the NiQuitin 4 mg arm. Although cough, throat tightness, headache, and dyspepsia occurred in more subjects while taking NSL4M than NiQuitin 4 mg, the overall numbers of subjects who experienced these adverse events were low.

During the mid-cycle meeting for this sNDA, the Clinical Pharmacology reviewer noted that this study was not conducted under the typical fed conditions recommended by the Agency and thus the effect of food for this formulation is not known.

3.3 INTEGRATED SUMMARY OF SAFETY

The safety data from the two pharmacokinetic studies NICTDP1076 and CO-160518135743-SCCT were included in the integrated summary of safety (ISS) pooled datasets. The safety population was defined as all subjects who were randomized and received at least one dose of study treatment. A total of 329 subjects received NiQuitin 4 mg and 324 received the 4 mg Nicorette Coated Ice Mint Lozenge. Each subject received single doses of the study products. A total of 331 subjects were included in the safety population for the pooled pharmacokinetic studies. A total of 13 subjects withdrew prematurely from the studies. No subjects discontinued either study due to an AE.

The safety population was made up of healthy adult smokers with a mean age of 30.5 years. Most subjects were white (97.3%) and females made up 54.1% of the population. Table 5 provides an overview of all treatment emergent adverse events (TEAEs), treatment-related AEs, nonfatal SAEs, deaths, and events leading to discontinuation by treatment, NiQuitin 4 mg and NSL4M 4 mg (proposed Nicorette Coated Ice Mint Lozenge 4 mg), for the pooled studies.

Table 5: Overview of Adverse Events for NiQuitin 4 mg and NSL4M 4 mg (Safety Population)

Adverse Event Type	NiQuitin™ 4 mg (N=329)		NSL4M 4 mg (N=324)	
All TEAEs	n (%)	nAE	n (%)	nAE
Any	116 (35.3)	190	135 (41.7)	229
Treatment-related	75 (22.8)	117	104 (32.1)	168
TEAEs leading to study discontinuation				
Any	0	0	0	0
Treatment-related	0	0	0	0
Nonfatal serious TEAEs				
Any	1 (0.3)	1	0	0
Treatment-related	0	0	0	0
AEs leading to death				
ANY	0	0	0	0
Treatment-related	0	0	0	0

Source: Sponsor's Table 13, ISS pg. 30

The percentage of any TEAEs and treatment-related TEAEs were higher with NSL4M 4 mg (proposed Nicorette Coated Ice Mint Lozenge 4 mg) than with the 4 mg reference product Nicorette Mint Lozenge (NiQuitin). A total of 116 (35.3%) subjects treated with 4 mg reference product and 153 (41.7%) subjects treated with Nicorette Coated Ice Mint Lozenge 4 mg experienced at least 1 TEAE. Treatment related AEs were experienced by 75 (22.8%) subjects treated with 4 mg reference product and 104 (32.1%) subjects treated with Nicorette Coated Ice Mint Lozenge 4 mg.

The most common TEAEs occurring in ≥2% of subjects in either treatment are provided in Table 6.

Table 6: Most Common (≥2% of subjects in either study treatment) Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class/ Preferred Term	NiQuitin™ 4 mg (n=329)		NSL4M 4 mg (n=324)	
	N (%)	nAE	N (%)	nAE
Number of subjects with at least 1 TEAE	116 (35.3)	190	135 (41.7)	229
Number of subjects with no AE	213 (64.7)		189 (58.3)	
Gastrointestinal disorders	46 (14.0)	59	69 (21.3)	88
Nausea	31 (9.4)	35	47 (14.5)	47
Dyspepsia	9 (2.7)	9	14 (4.3)	14
Respiratory, thoracic and mediastinal disorders	41 (12.5)	45	55 (17.0)	61
Throat irritation	21 (6.4)	22	26 (8.0)	26
Hiccups	7 (2.1)	7	17 (5.2)	17
Throat tightness	5 (1.5)	5	8 (2.5)	8
Nervous system disorders	31 (9.4)	32	33 (10.2)	33
Headache	26 (7.9)	27	27 (8.3)	27
Infections and infestations	20 (6.1)	20	14 (4.3)	14
Viral upper respiratory tract infection	16 (4.9)	16	12 (3.7)	12
Ear and labyrinth disorders	8 (2.4)	9	9 (2.8)	9
Vertigo	8 (2.4)	9	9 (2.8)	9

Source: Sponsor's Table 16, ISS pg. 34

The most frequently reported TEAEs that were greater in the proposed Nicorette Coated Ice Mint Lozenge 4 mg treatment as compared to the 4 mg reference product were nausea, headache, throat irritation, dyspepsia, vertigo, hiccups, and throat tightness.

One subject treated with NiQuitin 4 mg experienced a nonfatal SAE of spontaneous pneumothorax that was considered not treatment related. No subjects treated with the proposed Nicorette Coated Ice Mint Lozenge 4 mg experienced a death, nonfatal SAE, or TEAE that led to study discontinuation. No subjects treated with 4 mg reference product experienced a death or TEAE that led to study discontinuation.

Two pregnancies occurred in study NICTDP1076, and both resulted in withdrawal from the study. Both subjects chose to have induced abortions, which were not related to the study treatments. The pregnancies were reported and followed up in accordance with the protocol. The pregnancies were not counted as AEs, but were recorded as protocol deviations.

All TEAEs in the Phase 1 pooled studies were mild or moderate in intensity, except 5 severe TEAEs that occurred in 4 subjects. Subjects treated with NiQuitin 4 mg (Nicorette Mint Lozenge) experienced severe TEAEs of nausea and vomiting (both events in 1 subject) and headache (1 subject). Subjects treated with the proposed Nicorette Coated Ice Mint Lozenge 4 mg experienced severe TEAEs of nausea (2 subjects).

During the review of this sNDA, the Division received samples of the proposed product and a concern was raised about the similarity in appearance of the product to tablet dosage form. The appearance of the lozenge as a tablet may result in confusion by consumers who may accidentally swallow the product rather than letting it dissolve in the mouth. To further evaluate this potential of accidental swallowing of nicotine lozenges, a DMEPA Safety Evaluator conducted a search in FAERS for reports of wrong administration drug errors associated with the appearance of Nicorette lozenges and mini lozenges. Of the 503 cases for Nicorette lozenge and 188 cases for Nicorette mini lozenge, a text search was conducted using the following terms: "ingest," "swallow," "tablet," and "pill." There were 3 cases found for Nicorette lozenge and 1 case for Nicorette mini lozenge and were received between 2009 and 2011. These 4 cases suggest consumers accidentally swallowed the lozenges because the consumers thought the lozenges looked like oral tablets. The DMEPA Safety Evaluator concluded that these four cases are likely isolated incidents, because they occurred infrequently, and that the risk of accidental swallowing of the proposed lozenge can be mitigated via labeling.

Reviewer Comment:
The adverse events with the largest discrepancies between the proposed product and NiQuitin 4 mg were nausea, hiccups, throat irritation, and dyspepsia – more subjects experienced these with the proposed Nicorette Coated Ice Mint Lozenge. However, these adverse events are already known to occur with NRT use and do not indicate any new safety signals for the proposed product. Furthermore, the Drug Facts label informs consumers to:

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*
- *You have symptoms of an allergy reaction (such as difficulty breathing or rash)*

Also, the following statement is included in the Directions section:

- *Do not use more than one lozenge at a time or continuously use one lozenge after another since this may cause you hiccups, heartburn, or other side effects.*

Postmarketing Safety Data
The sponsor submitted a review of its postmarketing safety database. Cumulatively, a total of 6,057 Individual Case Safety Reports (ICSRs) were reported until December 31, 2017 for nicotine lozenges globally, of which 368 ICSRs were reported as serious and 5,689 ICSRs were reported as non-serious.

A total of 12,753 adverse events were reported from cumulative total of 6,057 ICSRs. The majority of the adverse events were reported from the four SOCs that constituted more than 50% (i.e. 69.9%) of the total number of adverse events reported. The following were SOCs of the adverse events for nicotine lozenges: gastrointestinal disorders (25.9%), injury, poisoning and procedural complications (15.6%), general disorders and administration site conditions (15.3%), and psychiatric disorders (13.2%). The commonly reported adverse events (i.e. ≥2%) were: nicotine dependence (n=826; 6.5%), nausea (n=705; 5.5%), intentional product use issue (n=697; 5.5%), drug ineffective (n=491; 3.9%), hiccups (n=301; 2.4%), malaise (n=287; 2.3%), Throat irritation (n=279; 2.2%), dyspepsia (n=264; 2.1%) and vomiting (n=264; 2.1%). All these commonly reported events are considered nonserious. Drug dependence and drug abuse were the most commonly reported serious adverse events. The sponsor reports that causality in these cases could not be determined due to the inherent dependence of the patients carried over from the patient's history of smoking.

4 CONCLUSION

The combined safety data from the two pharmacokinetic studies show that there were a higher number of adverse events with the new formulation than the original Nicorette lozenge – such as nausea, hiccups, throat irritation, and dyspepsia. However, these adverse events are consistent with known side effects associated with nicotine replacement therapy and are not indicative of new safety signals specific to the proposed product. Also, the proposed DFL includes statements to inform consumers of these potential side effects and when to ask a doctor about them.

The proposed newly formulated product has a similar appearance to a tablet. The similarity in appearance to a tablet may be confusing to consumers and lead to swallowing of the tablet rather than dissolving it in the mouth. Ingestion of the tablet may result in delay or reduction in absorption leading to reduced efficacy but is not a safety issue. The principal display panel clearly identifies the product in bold font as a "Lozenge" and directions on the DFL includes the statement in bold font "Do not chew or swallow lozenge." These statements adequately inform the consumers that the product is a lozenge and should not be chewed or swallowed.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENNY L KELTY
07/24/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-330/S-21

PHARMACOLOGY/TOXICOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 21330 Supplement 21
Supporting document/s:	Supporting Document Number (167) Response to Information Request (174) Response to Information Request (173)
Applicant's letter date:	02/22/2018 (167); 05/03/2018 (173); 06/05/2018 (174)
CDER stamp date:	02/22/2018 (167); 05/03/2018 (173); 06/05/2018 (174)
Product:	Nicotine Polacrilex Lozenges, 2 mg and 4 mg
Indication:	Reduction of withdrawal symptoms including nicotine craving associated with quitting smoking.
Applicant:	GlaxoSmithKline Consumer Healthcare
Review Division:	DNDP
Reviewer:	Jennie White, PhD
Supervisor/Team Leader:	Jane J Sohn, PhD
Division Director:	Teresa Michele, MD
Project Manager:	Alina Salvatore

Disclaimer

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1 Executive Summary

1.1 Introduction

The Applicant, GlaxoSmithKline Consumer Healthcare (GSKCH) submitted a Prior Approval Supplement (PAS) on February 22, 2018 under NDA 21330 for nicotine polacrilex (Nicorette) lozenges, 2 mg and 4 mg. The purpose of this PAS is to obtain marketing approval for a new flavor, "coated ice mint" and a smaller size lozenge to increase consumer appeal. The PAS includes a proposed reformulation of the previously approved product, Nicorette original lozenges (2 mg and 4 mg nicotine polacrilex).

A major amendment was submitted to the NDA on June 5, 2018, in response to an information request (IR), to support the safety of (b)(4) proposed novel impurities.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical studies were submitted in this supplement.

1.3 Recommendations

1.3.1 Approvability

Recommend approval from a nonclinical standpoint.

1.3.2 Additional Nonclinical Recommendations

Recommended communication to Application:

We recommend that you provide the quantitative composition of your formulation, including flavorings, to facilitate the review of future applications proposing a change in formulation. Further, provide the maximum daily intake for each excipient, including for each individual component of flavoring compounds. If you are relying upon a Drug Master File (DMF) to support a proposed flavoring, ensure that the DMF includes the quantitative composition of the flavoring.

1.3.3 Labeling

There are no nonclinical labeling changes in this supplement.

2 Drug Information

2.1 Drug

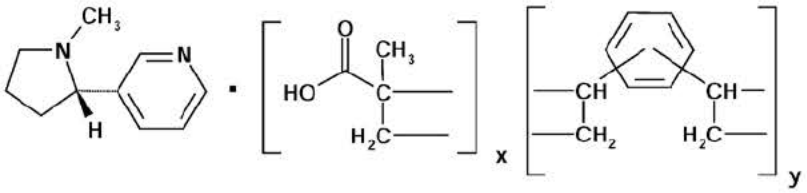
CAS Registry Number (Optional)
96055-45-7

Generic Name
Nicotine Polacrilex

Chemical Name
2-propenoic acid, 2-methyl-polymer with diethenylbenzene, complex with (S)-3-(1-methyl-2-pyrrolidinyl) pyridine; Methacrylic acid polymer with divinylbenzene, complex with nicotine

Molecular Formula/Molecular Weight
C10-H14-N2 (C10-H10.C4-H6-O2)x-/ 380.5288

Structure or Biochemical Description



Pharmacologic Class
Cholinergic Nicotinic Agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

DMF No. (b)(4).

2.3 Drug Formulation

The proposed reformulation is provided in the table below. The active ingredients are supported by previous formulations of currently marketed nicotine lozenge products.

Table 1. Proposed Formulation

Ingredient* in Proposed Drug Product (Nicorette Coated Ice Mint Lozenges)	Proposed Product
	(b)(4)
Nicotine polacrilex	
Mannitol	
Xanthan gum	
(b)(4)	
Sodium carbonate anhydrous	
Sucralose	
Acesulfame potassium	
Magnesium stearate	
Hypromellose	
Titanium dioxide	
Polysorbate 80	

(b)(4)

2.4 Comments on Novel Excipients

There are no novel excipients in the proposed reformulation. All the excipients are either supported by the previous formulation for this product, (b)(4) (see table 2 for details).

The (b)(4) according to a Quality submission dated February 13, 2008. The flavor in the approved product is specified at a level (b)(4)

However, for future submissions, the Applicant should provide specifications for each individual excipient (see Additional Nonclinical Recommendations).

Table 2. Inactive Ingredient Assessment

Inactive Ingredient in Proposed Drug Product (Nicorette Coated Ice Mint Lozenges)	Justification for Inclusion in Proposed Product
Mannitol	Found in previous formulation
Xanthan gum	Found in previous formulation
(b) (b)(4)	
Sodium carbonate anhydrous	

Sucralose	(b)(4)
Acesulfame potassium	
Magnesium stearate	
Polysorbate 80	

*See CMC review by Steve Hathaway, dated June 4, 2008.

2.5 Comments on Impurities/Degradants of Concern

For the proposed reformulation, most of the impurities are supported by existing shelf-life specifications of the previously approved product (Commit (nicotine polacrilex) lozenge 4 mg, NDA 21330), (b)(4) On May 1, 2018, the CMC team sent an IR requesting that the Applicant confirm whether the impurities were novel and to provide structures. The Applicant confirmed that these impurities were not specified in the previous formulation (see IR response dated May 3, 2018).

In the initial PAS submission, the Applicant did not adequately justify the inclusion of these new impurities at the proposed specification of NMT (b)(4). Instead, the Applicant stated that the proposed level of each impurity was below the ICH guidance for industry Q3B Impurities in Drug Products qualification threshold. All the impurities reported in the proposed reformulation fall at or below the relevant ICH Q3B qualification threshold, therefore, qualification with respect to general toxicology is not required. The potential for mutagenicity was not addressed in the submission, nor did they indicate whether they conducted a literature search. The Agency sent an IR to the Applicant on May 29, 2018; requesting that the Applicant provide a hazard assessment of the novel impurities:

> "We note that the total daily intake (TDI) of (b)(4) each of your novel impurities exceeds the threshold of toxicological concern for genotoxic impurities (b)(4) Post-approval submissions involving the drug product (e.g., change in impurity profile) include an evaluation of the potential risk associated with novel impurities. The hazard assessment involves an initial analysis of impurities by conducting database and literature searches for carcinogenicity and bacterial mutagenicity data in order to classify the impurities. If data for such a classification are not available, an assessment of Structure-Activity Relationships (SAR) that focuses on bacterial mutagenicity predictions is performed, and subsequent classification of the impurities."

The Applicant responded to the Agency IR on June (b)(4)

Appendix), and a hazard assessment based on ICH M7 guidelines. The CMC reviewer assigned to this application confirmed (conversation on June 6, 2018) (b)(4) The reviewer did not identify any additional mutagenicity or genotoxicity signals in the public domain.

The chemical structures for the (b)(4) proposed impurities were submitted to the Division of Applied Regulatory Science for a (Q)SAR analysis. The results of the analysis did not yield any structure activity relationships related to genotoxicity;therefore, (b)(4) to be negative for mutagenicity based on the Applicants (Q)SAR reports, review of the submitted literature (b)(4) and CDER's (Q)SAR conclusions. Since the MDI (b)(4) impurities is below the ICH Q3B qualification threshold, the need for qualification studies to address non-genotoxic endpoints will not be triggered by this PAS.

Table 3. Impurity Assessment

Impurity	Proposed Product			Previously approved product	Q3B Qualification Threshold^^ (mg)	ICH M7 Threshold (mg/day)
	Shelf Life Specification	Quantity Per Unit (mg)	Maximum Daily Intake (mg)*	Shelf Life Specification		
(b)(4)					0.4	0.0015
					0.4	0.0015
					0.4	0.0015
					0.4	0.0015
					0.4	0.0015
					0.4	0.0015
					0.4	0.0015
(b)(4)						

2.6 Proposed Clinical Population and Dosing Regimen

The proposed consumer population is adult smokers, the maximum recommended daily dose is 20 lozenges. No new clinical trials are proposed in this review cycle.

2.7 Regulatory Background

The Agency approved Commit™ (nicotine polacrilex lozenge, 2 mg and 4 mg) for nonprescription use on December 31, 2002.

Since the original NDA approval, the Applicant has obtained approval for marketing additional flavored reformulations (cappuccino, mint, and cherry) and has also obtained approval for marketing a "mini" lozenge.

On October 25, 2013, the Applicant submitted a request (b)(4) In a face to face meeting, the Agency advised GSK that bioequivalence studies in a fasted state would be required to establish an adequate bridging program and requested a detailed qualitative and quantitative information for excipients in their regulatory submission, and referred them to the excipients guidance.

3 Studies Submitted

3.1 Studies Reviewed

(b)(4)

(b)(4)

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

None.

4 Pharmacology

None submitted.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

None submitted.

6 General Toxicology

None submitted.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: (b)(4)

Study no.:	N/A
Study report location:	(b)(4)
Conducting laboratory and location:	Not listed, although the publication is from the " (b)(4)
Date of study initiation:	Not listed
GLP compliance:	Not listed, but most likely not compliant.
QA statement:	None.
Drug, lot #, and % purity:	(b)(4), purity not listed

Key Findings:

- (b)(4) did not produce any dose-response with respect to mean revertants. Although this negative result is reassuring, the results are of limited utility due to several validity concerns and the limited information provided in the summary report.
- (b)(4) induced reversible DNA damage in an E. coli pol A- mutant compared to the wild-type strain. It is not clear how this assay translates to human risk for cancer.

Eight (8) pages have been redacted as (b)(4), Trade Secret/CCI, immediately following this page.

Conclusion

The assays reviewed herein were conducted in 1982, just a few years after the development of the Ames assay, and before many of the current standards for validity were established, therefore, they are of limited utility. Further, because this review uses a summary report, rather than a full study report, the full data sets that are necessary for a complete review are not available, nor can they be requested.

In conclusion, (b)(4) at doses from (b)(4) metabolic activation did not produce a dose-dependent increase in mean revertants per plate. Although these results are reassuring, the assay is of limited utility for the following reasons:

1. There are several validity concerns (see validity section for full description) including an excessively high dose, lack of adequate controls for all strains and test conditions, no contemporary historical control data, and a lack of complimentary strain set.
2. A full study report was not provided; therefore, the reviewer cannot evaluate the results against criteria for a positive response.

(b)(4) administered at (b)(4) This assay is not recommended by the FDA and is of limited utility for the following reasons:

1. This assay is not recommended by the FDA for inclusion in a standard genotoxicity battery, guidelines for testing have not been published by any Agency with which the FDA collaborates on developing standards, and there is a paucity of literature available in the public domain. The only methodology paper available is the one authored by Rosenkranz et al (1980) (b)(4).
2. There are several validity concerns, including lack of dose justification, lack of a metabolically activated arm in the confirmatory assay, limited positive response criteria, and no historical control data.

8 Carcinogenicity

None submitted.

9 Reproductive and Developmental Toxicology

None submitted.

10 Special Toxicology Studies

None submitted.

11 Integrated Summary and Safety Evaluation

GlaxoSmithKline Consumer Healthcare (GSK) has submitted a Prior Approval Supplement (PAS) under NDA 21330 for nicotine polacrilex (Nicorette) lozenges, 2 mg and 4 mg. All the ingredients and impurities found in the proposed formulation are supported by the previously approved product or by regulatory clearances, with the

exception of the following (b)(4) impurities: (b)(4) . The maximum daily intake for (b)(4) impurities is calculated to be (b)(4) µg/day (b)(4) based on a maximum daily dose of 20 lozenges. The MDI for the impurities is below the ICH Q3B qualification threshold of 0.4 mg/day, therefore, no qualification studies with respect to general toxicology will be triggered by this PAS. With respect to mutagenicity, however, the MDI's are above the ICH M7 threshold for mutagenic impurities (1.5 µg/day, see table 6), therefore, the potential for mutagenicity must be evaluated.

(b)(4)

The structures for (b)(4) were submitted to the Division of Applied Regulatory Sciences (DARS) for a (Q)SAR analysis. Based on a (Q)SAR analysis, (b)(4) impurities were negative for structural alerts for mutagenicity (see Appendix).

The Applicant submitted a hazard assessment with their own (Q)SAR evaluation of (b)(4) impurities and single reference on the genotoxicity (b)(4) . The Applicant's (Q)SAR report also predicted all three impurities to be negative for mutagenicity. Based on a review of the reference provided in the hazard assessment, (b)(4) doses from (b)(4) (b)(4) metabolic activation did not produce a dose-dependent increase in mean revertants per plate. Although these results are reassuring, the assay is of limited utility due to several validity concerns. (b)(4) administered (b)(4) induced reversible DNA damage in both tests. This assay is not recommended by the FDA and is also of limited utility due to several validity concerns.

In summary, a (Q)SAR analysis of (b)(4) yielded no structural alerts for mutagenicity (see Appendix), therefore no genotoxicity studies will be required. Further, since the MDI's (b)(4) for all impurities are below the ICH Q3B Qualification Threshold (0.4 mg/day), no general toxicity studies will be required. No further action is indicated for these impurities. The PAS is recommended for approval from a nonclinical standpoint.

12 Appendix/Attachments

References:

Ames B, McCann J, and Yamasaki E (1975). Methods for Detecting Carcinogens and Mutagencs with the Salmonella/ Mammalian Microsome Mutagenicity Test. Mutation Research 31, pp 347-364.

Leifer Z, Hyman J, Rosenkranz HS (1980). Determination of Genotoxic Activity Using DNA Polymerase-Deficient and -Proficient *E. coli*. In: Stich H.F., San R.H.C. (eds) Short-Term Tests for Chemical Carcinogens. Topics in Environmental Physiology and Medicine. Springer, New York, NY.

Pant K**,** Bruce S**,** Sly J**,** Klug Laforce M**,** Springer S**,** Cecil M**,** Andrus E**,** Dakoulas E**,** Wagner VO 3rd**,** Hewitt NJ, Kulkarni R (2016). Bacterial mutagenicity assays: Vehicle and positive control results from the standard Ames assay, the 6- and 24-well miniaturized plate incorporation assays and the Ames II™ assay. Environ Mol Mutagen. 57(6) pp 483-96.

(b)(4)

Two (2) pages have been removed as (b)(4), Trade Secret/CCI, immediately following this page.

Appears This Way

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENNIFER J WHITE
08/02/2018

JANE J SOHN
08/02/2018
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-330/S-21

CLINICAL PHARMACOLOGY REVIEW

Office of Clinical Pharmacology Review

NDA or BLA Number	21330; Supplement 021 for a new Nicorette Lozenge (Coated Ice Mint flavor)
Link to EDR	\\CDSESUB1\EVSPROD\NDA021330\0076 \\CDSESUB1\EVSPROD\NDA021330\0083
Submission Date	2/22/18; 4/25/18; PDUFA date: 6/22/18
Submission Type	Chemistry, Manufacturing, and Controls (CMC) with Labeling -4 months
Brand Name	Nicotine Lozenges
Generic Name	Nicotine Polacrilex
Dosage Form and Strength	Lozenge; 2 and 4 mg
Route of Administration	Oral
Proposed Indication	Reduce withdrawal symptoms including nicotine craving associated with quitting smoking
Dosage Regimen	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 □ begin using the lozenge on your quit day □ if you smoke your first cigarette more than 30 minutes after waking up, (b)(4) □ if you smoke your first cigarette within 30 minutes of waking up, use (b)(4) according to the following 12-week schedule:

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to12
1 lozenge every 1 to 2 h	1 lozenge every 2 to 4 h	1 lozenge every 4 to 8 h

□ 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 (Applicant suggestion: delete *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 (Applicant suggestion: delete *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. □ it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.
Applicant	GlaxoSmithKline Consumer Healthcare
Associated IND	-
OCP Reviewer	David Lee, Ph.D.
OCP Team leader	Yun Xu, Ph.D.

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in the current supplement application, 021, NDA 21330, for Nicorette Lozenge (Coated Ice Mint flavor), submitted on 2/22/18. From a clinical pharmacology perspective, the information submitted in the supplement NDA is acceptable. No further communication is necessary with the Applicant at this point.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The results from Study CO-160518135743-SCCT, a single dose fasted 4 mg study, provided pivotal evidence that Nicorette Coated Ice Mint Lozenge 4 mg (referred to as Nicorette Peppermint Lozenge (NPL) in the study) and Nicorette Original/Mint Lozenge (NML) 4 mg (United States reference product) were bioequivalent [90% CIs were within the accepted limits of 80% to 125% for the geometric least squares means ratios for baseline-corrected AUC0-t, AUC0-inf, and Cmax (cAUC0-t, cAUC0-inf, and cCmax) parameters]. (b)(4). The reader is referred to Biopharmaceutics Review regarding the approvability discussion of 2-mg strength.
General dosing instructions	There are no changes to Nicorette dosing instructions in this supplement.
Dosing in patient subgroups (intrinsic and extrinsic factors)	There are no changes to Nicorette dosing instructions in this supplement.
Labeling	The mean oral dissolution time for NCIM is approximately 13 minutes (Study CO-160518135743-SCCT, a fasted 4 mg). To be consistent with Nicorette Mini Mint lozenge, the dissolution time is not proposed to be added on the Nicorette Coated Ice Mint Lozenge label. The Applicant's proposal is acceptable.
Bridge between the to-be-marketed and clinical trial formulations	For 4 mg, the final to-be-marketed formulation was used in the bioequivalence study.
Other (specify)	Not applicable.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

The Applicant, GlaxoSmithKline Consumer Healthcare (GSKCH), has submitted Prior Approval Supplement (PAS) 021, Chemistry, Manufacturing, and Controls (CMC) with Labeling, for a new formulation of Nicorette (nicotine polacrilex) Lozenges 2 mg and 4 mg as a 505(b)(1) submission. The proposed lozenge is a coated, mint flavored lozenge and is referred to as Nicorette Coated Ice Mint lozenges (b)(4) which have been co-developed by GSKCH (b)(4) (commercialization of the product)

The Applicant stated that the proposed Nicorette Coated Ice Mint ("NCIM") lozenges contain the same active ingredient (nicotine polacrilex) and the same strengths (2 mg and 4 mg) as the currently approved Nicorette original lozenges (NDA 021330). However, the proposed NCIM lozenges are coated, have a different formulation and are different in shape, size and weight compared to the Nicorette original lozenges. The Applicant stated that the proposed NCIM lozenges are intended to provide a lozenge product in between the Nicorette large original lozenge and Nicorette mini lozenges (NDA 023660). The Applicant has cross referenced the following documents in this supplement: DMF (b)(4) DMF (b)(4) NDA 022360.

Information submitted in the current Supplement 021:

In the current CMC with Labeling supplement, with respect to clinical pharmacology, the Applicant has submitted two studies for the registration of the proposed NCIM lozenge based on: 1) the 'fasted' study (CO-160518135743-SCCT) between the proposed NCIM lozenge 4 mg and the listed Nicorette Original Lozenge 4 mg (NDA 021330) currently marketed in the United States (US), and, 2) the 'fed' BE study (Study NICTDP1076) which assessed clinical formulations of 2 and 4 mg formulations (i.e., buffering capacity) compared to NiQuitin™ ("NiQuitin") lozenges (European marketed brand identical to the reference listed Nicorette Mint Lozenge in the US). (b)(4). The reader is referred to Biopharmaceutics Review regarding the approvability discussion of 2 mg strength.

Discussion regarding the 'fed' Study NICTDP1076

Study NICTDP1076 was labeled and described by the Applicant as a 'fed' study. However, after considering the study design, it was determined that this study was not a typical food study recommended by the Agency. An Information Request (IR) was sent to the Applicant on 4/24/18 and the Applicant submitted their reply on 4/26/18 as follows:

> For Study NICTDP1076, a 'fed' study, provide the following information:
>
> 1. Elaborate if the subjects were fasted overnight at least 10 hours before they consumed breakfast at home;
>
> GSK Response:

In study NICTDP1076, there were no restrictions or requirements for the study subjects regarding overnight fasting before the at-home breakfast. In addition, no information was collected from the subjects regarding fasting the night before their scheduled study visit.

2. Contents of the breakfast which the subjects consumed at home prior to arrival at the trial site;

GSK Response:
It was requested that the subjects have breakfast at home on the morning of their scheduled study visit, however the type of food was not defined. Additionally, no information about food intake prior to administration of the test product was collected.

3. Provide the time elapsed between the breakfast consumed at home and nicotine product administration at the trial site.

GSK Response:
The timing of the at-home breakfast (in relation to drug administration) was not defined. However, the subjects were instructed not eat or drink from 15 minutes before until 60 minutes after the start of drug administration.

Therefore, it is recommended that results from Study NICTDP1076 are considered as a *supportive* information.

Additionally, the study results from Study NICTDP1076 have minimal- to no- impact on the approvability of the current CMC PAS since:

1) there is no 'food' effect information in the current Nicorette lozenge Labels (original and mini lozenges);
2) it appears that food effect studies were not submitted in the original Nicorette lozenge submission;
3) the Office of Generic Product recommends one fasted bioequivalence study for a drug specific nicotine lozenge products; and,
4) the results from Study CO-160518135743-SCCT, a fasted 4 mg study, provides adequate information without confounding factors such as food effect in comparing the NCIM and the original Nicorette lozenge (N 21330).

Labeling changes proposed:

The proposed NCIM lozenges have identical labeling and use instructions to the current Nicorette lozenge products.

The currently approved Nicorette Original lozenges (NDA 021330) reference oral dissolution time in the Directions portion of Drug Facts. However, currently approved Nicorette Mini Mint lozenges do not reference the oral dissolution time (reference to dissolution time was deleted from

all the Nicorette Mini lozenges 2 mg and 4 mg labeling, including User's Guides through a Prior Approval Supplement submitted March 2012).

The mean oral dissolution time for NCIM is approximately 13 minutes (Study CO-160518135743-SCCT, a fasted 4 mg). To be consistent with Nicorette Mini Mint lozenge, the dissolution time is not proposed to be added on the label (Table 1). The Applicant's proposal is acceptable.

Table 1 Summary of Differences in the Directions Section of Drugs Facts and User's Guide

Labeling	Statements in the currently marketed Nicorette Original Lozenge (NDA 021330)	Statements in the currently marketed Nicorette Mini Mint Lozenge (NDA 022360)	Statements in the proposed Nicorette Coated Ice Mint lozenge labeling
Drug Facts *(Directions)*	"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."	"place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. Do not chew or swallow lozenge."	"place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. Do not chew or swallow lozenge."
Drug Facts *(Directions)*	"occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20 -30 minutes)"	"occasionally move the lozenge from one side of your mouth to the other until completely dissolved"	"occasionally move the lozenge from one side of your mouth to the other until completely dissolved"
User's Guide: USING Nicorette LOZENGES PROPERLY section	1) Remove the Nicorette Lozenge from the immediate container. Place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20-30 minutes). Minimize swallowing. Do not chew or swallow the lozenge. You may feel a warm or tingling sensation. 2) Occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20 -30 minutes)"	1) Remove the Nicorette mini Lozenge from the immediate container. Place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. Do not chew or swallow the lozenge. You may feel a warm or tingling sensation. 2) Occasionally move the lozenge from one side of your mouth to the other until completely dissolved.	1) Remove the Nicorette Lozenge from the immediate container. Place the lozenge in your mouth and allow the lozenge to slowly dissolve. Minimize swallowing. Do not chew or swallow the lozenge. You may feel a warm or tingling sensation. 2) Occasionally move the lozenge from one side of your mouth to the other until completely dissolved.

Study CO-160518135743-SCCT findings: 'pivotal' information

The results from Study CO-160518135743-SCCT provided pivotal evidence that, following a single dose, Nicorette Coated Ice Mint Lozenge 4 mg (referred to as Nicorette Peppermint Lozenge (NPL) in this study) and Nicorette Original/Mint Lozenge (NML) 4 mg (United States reference product) were bioequivalent [Table 3: nicotine baseline corrected-arithmetic means (standard deviation (SD) pharmacokinetic parameters; Table 3: 90% CIs were within the accepted limits of 80% to 125% for the geometric least squares means ratios for baseline-corrected AUC0-t, AUC0-inf, and Cmax (cAUC0-t, cAUC0-inf, and cCmax) parameters].

Table 2 Mean Arithmetic [(standard deviation (SD)] Nicotine single dose, NPL 4 mg, Baseline-corrected Pharmacokinetic Parameters, Study CO-160518135743-SCCT

PK parameter	**NML 4 mg** (n=220-221)	**NPL 4 mg** (n=217-218)
cC_{max} (ng/mL)	8.37 (3.49)	7.97 (3.18)
$cAUC_t$ (ng/mLxh)	28.98 (12.38)	28.06 (11.96)
$cAUC_{inf}$ (ng/mLxh)	31.79 (13.69)	30.77 (13.13)
$cAUC_{extrap}$ (%)	9.0 (3.2)	9.0 (3.0)
t_{max}* (h)	0.67 (0.17-2.00)	0.83 (0.17-3.00)
λ_z (h^{-1})	0.24 (0.06)	0.24 (0.06)
$t_{1/2}$ (h)	3.11 (0.99)	3.08 (0.82)

Test Product: Nicorette Peppermint Lozenge (NPL) 4 mg. Nicorette Coated Ice Mint Lozenges were referred to as Nicorette Peppermint Lozenge (NPL) 4 mg in this study; Reference Product: Nicorette Mint Lozenge (NML) 4 mg.
Source: CSR CO-160518135743-SCCT Tables 14.2.2.1 and 14.2.2.2; * Median (Min – Max)
Same as Table 9, Section 3.2.1 below

Table 3 Pharmacokinetic Parameters Estimated Ratios of Geometric Means Nicotine Single Dose, NPL 4 mg, Study CO-160518135743-SCCT

	NPL 4 mg vs. NML 4 mg (n=211)	
	Ratio (%)	**90% CI (%)**
cCmax	94.9	91.9 – 98.1
cAUCt	95.6	93.2 – 98.0
cAUCinf	95.6	93.3 – 97.9

Test Product: Nicorette Peppermint Lozenge (NPL) 4 mg. Nicorette Coated Ice Mint Lozenges were referred to as Nicorette Peppermint Lozenge (NPL) 4 mg in this study; Reference Product: Nicorette Mint Lozenge (NML) 4 mg.
Source: CSR CO-160518135743-SCCT, Table 14.2.3
Same as Table 11, Section 3.2.1 below

Study NICTDP1076 findings: 'supportive' information

The results from Study NICTDP1076 showed that, following a single dose, Nicorette Strongmint Lozenge (NSL) 2 mg low level of buffer capacity clinical formulation, NSL2L, and, a comparator product, NiQuitin 2 mg, were bioequivalent [Table 4: nicotine baseline corrected-arithmetic means (standard deviation (SD) pharmacokinetic parameters; Table 5: 90% CIs were within the accepted limits of 80% to 125% for the geometric least squares means ratios for baseline-corrected AUC0-t, AUC0-inf, and Cmax (cAUC0-t, cAUC0-inf, and cCmax) parameters].

Table 4 Mean Arithmetic [(standard deviation (SD)] Nicotine Single Dose, NSL2L, Baseline-corrected Pharmacokinetic Parameters, Study NICTDP1076

PK parameter	**NSL2L 2 mg** (n=94)	**NiQuitin 2 mg** (n=96)
cC_{max} (ng/mL)	4.9 (1.7)	5.4 (1.9)
$cAUC_t$ (ng/mLxh)	13.7 (7.0)	14.9 (6.4)
$cAUC_{inf}$ (ng/mLxh)	16.0 (8.6)	16.9 (7.0)
t_{max}* (h)	0.67 (0.13-2.0)	0.5 (0.25-2.0)
$t_{1/2}$ (h)	3.1 (1.2)	2.9 (1.0)

Source: CSR NICTDP1076 Table 14.2.2; * Median (min-max)
Same as Table 14, Section 3.2.2 below

Table 5 Pharmacokinetic Parameters Estimated Ratios of Geometric Means Nicotine Single Dose 2 mg, NSL2L, Study NICTDP1076

	NSL2L vs. NiQuitin™ lozenge 2 mg (n=94-96)	
	Ratio	Interval
cC_{max}	89.3%	84.2-94.8%
$cAUC_t$	90.5%	86.1-95.2%
cAUC□	92.1%	87.7-96.6%

Source: CSR NICTDP1076 Table 14.2.2
Same as Table 15, Section 3.2.2 below

Following a single dose, NSL 4 mg medium level of buffer capacity and high level of buffer capacity formulations, NSL4M and NSL4H, respectively, and, NiQuitin 4 mg, were bioequivalent (Table 6). However, NSL 4 mg low level of buffer capacity, NSL4L, was not bioequivalent to NiQuitin 4 mg (Table 6).

Table 6 Pharmacokinetic Parameters Estimated Ratios of Geometric Means Nicotine Single Dose 4 mg, NSL4L, NSL4M and NSL4H, Products, Study NICTDP1076

	NSL4L vs. NiQuitin™ lozenge 4 mg (n=46)		**NSL4M vs. NiQuitin™ lozenge 4 mg (n=97-99)**		**NSL4H vs. NiQuitin™ lozenge 4 mg (n=50)**	
	Ratio	**Interval**	**Ratio**	**Interval**	**Ratio**	**Interval**
cC_{max}	78.5%	*71.5*-86.2%	85.5%	81.0-90.4%	90.8%	82.9-99.4%
$cAUC_t$	80.5%	*72.8*-89.0%	88.1%	83.9-92.4%	90.6%	82.1-99.9%
$cAUC_\infty$	80.6%	*72.3*-90.0%	88.7%	84.7-92.9%	93.3%	83.9-103.8%

Source: CSR NICTDP1076 Table 14.2.2

Biowaiver request for 2 mg strength

(b)(4) (b)(4) . It is noted that 2 mg coated ice mint was compared with NiQuitin Lozenges (Study NICTDP 1076). The Applicant stated that NiQuitin Lozenges 2 mg and 4 mg marketed in Europe are identical to the Nicorette Original Lozenges 2 mg and 4 mg marketed in the US. Study

2.1 Pharmacology and Clinical Pharmacokinetics

2.1.1. What is the proposed indication?

There are no changes to Nicorette indication in this supplement. The indication for Nicorette is to "reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking."

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

There are no changes to Nicorette dosing instructions in this supplement. The following overall dosing recommendations are proposed according to the 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.
□ before using this product, read the enclosed User's Guide for complete directions and other important information
□ begin using the lozenge on your quit day
□ if you smoke your first cigarette within 30 minutes of waking up, use 4 mg nicotine lozenge
□ if you smoke your first cigarette more than 30 minutes after waking up, use 2 mg nicotine lozenge according to the following 12-week schedule (Table 7):

Table 7 Dosage administration

Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to12
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. 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
 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.
it is important to complete treatment. If you feel you need to use the lozenge for a longer period to keep from smoking, talk to your health care provider.

2.2.2 (b)(4)

(b)(4) The reader is referred to Biopharmaceutics Review regarding the approvability discussion of 2 mg strength.

2.3 Outstanding Issues

There are no outstanding issues.

2.4 Summary of Labeling Recommendations

The proposed deletion of the dissolution time is acceptable. There are no Labeling recommendations at this time.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

3.1.1 Nicorette Mint formulation composition

The Applicant provided the following qualitative composition of Nicotine Coated Ice Mint lozenges in Table 8 below.

Table 8 Qualitative Composition of Nicotine Coated Ice Mint Lozenges (2 mg and 4 mg)

Component	Reference to Quality Standard	Function
(b)(4)		
Nicotine polacrilex[1]		
Mannitol		
Xanthan Gum		
(b)(4)		
Sodium carbonate anhydrous		
Sucralose		
Acesulfame Potassium		
Magnesium Stearate		
(b)(4)		
(b)(4)		
(b)(4)		
(b)(4)		
Polysorbate 80		
(b)(4)		
(b)(4)		

3.1.2 What is proposed route of administration?

The proposed route of administration for Nicorette Coated Ice Mint Lozenges is oral.

3.2 Clinical Pharmacology Review Questions

3.2.1 To what extent does the available clinical pharmacology information from Study CO-160518135743-SCCT provide pivotal or supportive evidence?

Summary: The results from Study CO-160518135743-SCCT provided pivotal evidence that, following a single dose, Nicorette Coated Ice Mint Lozenge 4 mg (referred to as Nicorette Peppermint Lozenge (NPL) in this study) and Nicorette Original/Mint Lozenge (NML) 4 mg

(United States reference product) were bioequivalent [90% CIs were within the accepted limits of 80% to 125% for the geometric least squares means ratios for baseline-corrected AUC0-t, AUC0-inf, and Cmax (cAUC0-t, cAUC0-inf, and cCmax) parameters].

Reviewer comment: The results from Study CO-160518135743-SCCT are acceptable.

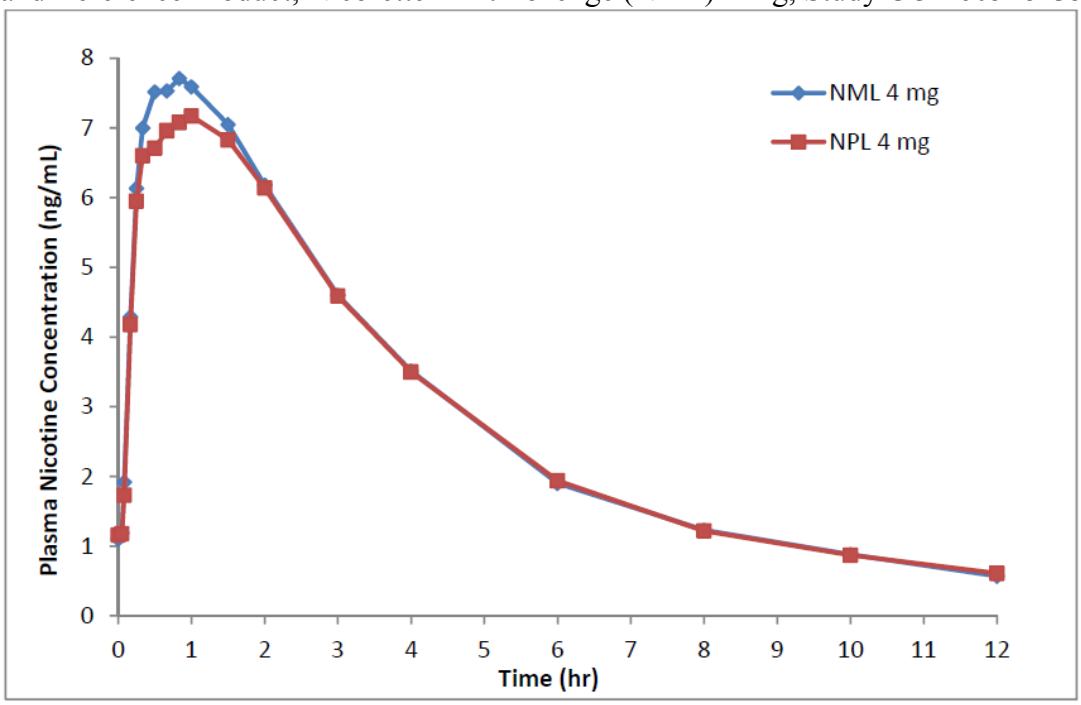
Study CO-160518135743-SCCT was a single-dose, randomized, open-label, fasting, 2-period crossover, Phase 1 bioequivalence study conducted in 227 healthy adult subjects (smokers of at least 10 cigarettes per day and for at least one year preceding inclusion; study was conducted at 2 clinical sites in Sweden). This study compared the proposed Nicorette Coated Ice Mint Lozenge 4 mg (referred to as Nicorette Peppermint Lozenge (NPL) in this study) and Nicorette Original/Mint Lozenge (NML) 4 mg (United States [US] reference listed drug). Subjects were instructed to place the lozenge in their mouth, to occasionally move it from side to side until complete dissolution, and to not chew or swallow the lozenges. Talking was not allowed during the dissolution time. Each subject abstained from any nicotine-containing products for 12 hours before each study treatment, a minimum 10-hour overnight fast including an overnight stay at the clinic. All subjects continued to fast and refrained from lying down during the first 4 hours after dosing. The washout period between treatments was at least 36 hours.

Blood samples were taken at pre-dose, 3, 5, 10, 15, 20, 30, 40, 50, and 60 min, and, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours post dose. The dissolution time for treatments were collected. Blood samples were centrifuged at approximately (b)(4) for (b)(4) minutes at (b)(4). Each plasma sample was transferred to an appropriately labeled screw-capped polypropylene tube (b)(4) (b)(4) (b)(4) until transport to the bioanalytical lab for analysis. Samples were analyzed at the (b)(4), (b)(4). Nicotine in plasma was analyzed using a validated analytical method in compliance with (b)(4) standard operating procedures. The mass spectrometric method was a GC-MS method validated per current guidelines for Bioanalytical method validation (validated between (b)(4) ng/mL; Lower Limit of Quantification (LLOQ) of 0.5 ng/mL; to eliminate contamination from the environment, the laboratories and its staff were nicotine free. Glassware used in the preparation of calibration standards, quality control samples, sample preparation etc. were all new and washed before use per the method).

For pharmacokinetic analysis, nicotine Cmax and AUC values were corrected for nicotine baseline concentrations, e.g., cCmax, cAUCinf, etc., for each subject using the subject's pre-dose concentration (C_0). Data from treatment visits with baseline nicotine concentrations exceeding 5 ng/mL were excluded (4 subjects-Subj ID (b)(6) and (b)(6)-had baseline plasma nicotine concentration higher that 5 ng/mL for one treatment) from the analysis.

The mean nicotine plasma concentration profiles for both treatments plotted over 12 hours are presented in Figure 1.

Figure 1 Mean Nicotine Plasma Concentration vs. Time Profiles over 12 hours for Nicorette Coated Ice Mint Lozenges [referred to as Nicorette Peppermint Lozenge (NPL) 4 mg in this study] and Reference Product, Nicorette Mint Lozenge (NML) 4 mg, Study CO-160518135743-SCCT



Test Product: Nicorette Peppermint Lozenge (NPL) 4 mg. Nicorette Coated Ice Mint Lozenges were referred to as Nicorette Peppermint Lozenge (NPL) 4 mg in this study; Reference Product: Nicorette Mint Lozenge (NML) 4 mg.
Source: CSR CO-160518135743-SCCT Figure 1

Nicotine baseline corrected-arithmetic means [(standard deviation (SD)] of 'cCmax', 'cAUCt' and 'cAUCinf' pharmacokinetic parameters are presented with in Table 9.

Table 9 Mean Arithmetic [(standard deviation (SD)] Nicotine Single Dose, NPL 4 mg, Baseline-corrected Pharmacokinetic Parameters, Study CO-160518135743-SCCT

PK parameter	**NML 4 mg** (n=220-221)	**NPL 4 mg** (n=217-218)
cC_{max} (ng/mL)	8.37 (3.49)	7.97 (3.18)
$cAUC_t$ (ng/mLxh)	28.98 (12.38)	28.06 (11.96)
$cAUC_{inf}$ (ng/mLxh)	31.79 (13.69)	30.77 (13.13)
$cAUC_{extrap}$ (%)	9.0 (3.2)	9.0 (3.0)
t_{max}* (h)	0.67 (0.17-2.00)	0.83 (0.17-3.00)
λ_z (h^{-1})	0.24 (0.06)	0.24 (0.06)
$t_{1/2}$ (h)	3.11 (0.99)	3.08 (0.82)

Test Product: Nicorette Peppermint Lozenge (NPL) 4 mg. Nicorette Coated Ice Mint Lozenges were referred to as Nicorette Peppermint Lozenge (NPL) 4 mg in this study; Reference Product: Nicorette Mint Lozenge (NML) 4 mg.
Source: CSR CO-160518135743-SCCT Tables 14.2.2.1 and 14.2.2.2; * Median (Min – Max)

Nicotine geometric means of cCmax, cAUCt and cAUCinf and statistical analysis (mean ratio and 90% confidence intervals) of the log-transformed plasma PK parameters of nicotine are presented in Tables 10 and 11, respectively.

Table 10 Pharmacokinetic Parameters Observed Geometric Means (CV%) Nicotine Single Dose, NPL 4 mg, Study CO-160518135743-SCCT

PK parameter	**NML 4 mg** (n=220)	**NPL 4 mg** (n=217)
cC_{max} (ng/mL)	7.80 (41.67)	7.47 (39.87)
$cAUC_t$ (ng/mLxh)	26.82 (42.71)	25.94 (42.62)
$cAUC_{inf}$ (ng/mLxh)	29.49 (43.07)	28.52 (42.66)

Test Product: Nicorette Peppermint Lozenge (NPL) 4 mg. Nicorette Coated Ice Mint Lozenges were referred to as Nicorette Peppermint Lozenge (NPL) 4 mg in this study; Reference Product: Nicorette Mint Lozenge (NML) 4 mg.
Source: CSR CO-160518135743-SCCT, Table 14.2.3

Table 11 Pharmacokinetic Parameters Estimated Ratios of Geometric Means Nicotine Single Dose, NPL 4 mg, Study CO-160518135743-SCCT

	NPL 4 mg vs. NML 4 mg (n=211)	
	Ratio (%)	**90% CI (%)**
cC_{max}	94.9	91.9 – 98.1
$cAUC_t$	95.6	93.2 – 98.0
$cAUC_{inf}$	95.6	93.3 – 97.9

Test Product: Nicorette Peppermint Lozenge (NPL) 4 mg. Nicorette Coated Ice Mint Lozenges were referred to as Nicorette Peppermint Lozenge (NPL) 4 mg in this study; Reference Product: Nicorette Mint Lozenge (NML) 4 mg.
Source: CSR CO-160518135743-SCCT, Table 14.2.3

Table 12 provides subjects' complete dissolution times of the tablets in the mouth.

Table 12 Dissolution Time (minutes) Nicotine Single Dose, NML and NPL 4 mg, Study CO-160518135743-SCCT

	Mean	**SD**	**Median**	**Min**	**Max**
NML 4 mg	19.80	11.39	17.0	5	107
NPL 4 mg	12.92	5.88	12.0	3	44

Test Product: Nicorette Peppermint Lozenge (NPL) 4 mg. Nicorette Coated Ice Mint Lozenges were referred to as Nicorette Peppermint Lozenge (NPL) 4 mg in this study; Reference Product: Nicorette Mint Lozenge (NML) 4 mg.
Source: CSR CO-160518135743-SCCT, Table 14.2.4

The bioequivalence analysis results indicated that Nicorette Coated Ice Mint Lozenges (referred to as Nicorette Peppermint Lozenge (NPL) 4 mg in this study) and reference product, Nicorette Mint Lozenge (NML) 4 mg, were bioequivalent.

3.2.2 To what extent does the available clinical pharmacology information from Study NICTDP1076, a 'fed' study, provide pivotal or supportive evidence?

Summary: The results from Study NICTDP1076 provide supported evidence for Nicorette Coated Ice Mint Lozenge 2 and 4 mg (referred to as Nicorette Strongmint Lozenge (NSL) in this study) as: 1) (b)(4), 2) Study CO-160518135743-SCCT provided pivotal evidence for 4 mg. The reader is referred to Biopharmaceutics Review regarding the approvability discussion of 2 mg strength.

The results, however, showed that, following a single dose, NSL 2 mg low level of buffer capacity formulation, NSL2L, and a comparator product, NiQuitin 2 mg, were bioequivalent.

Following a single dose, NSL 4 mg medium level of buffer capacity and high level of buffer capacity formulations, NSL4M and NSL4H, respectively, and, reference product, NiQuitin 4 mg, were bioequivalent. However, NSL 4 mg low level of buffer capacity, NSL4L, was not bioequivalent to NiQuitin 4 mg.

Reviewer comment: The results from Study NICTDP1076 are acceptable.

Note: *'fed': not a typical food study recommended by the Agency. See discussion above, Section 2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT.

Study NICTDP1076 was a single-dose, randomized, open-label, 'fed'*, 5-period crossover, Phase 1 study conducted in 104 healthy adult subjects (smokers of at least 10 cigarettes per day and for at least one year preceding inclusion; study was conducted at 2 clinical sites in Sweden). This study compared (Table 13) the (b)(4) Nicorette Coated Ice Mint Lozenges [referred to as Nicorette Strongmint Lozenge (NSL) in this study] 2 and 4 mg and NiQuitin 2 and 4 mg [NiQuitin lozenges (European marketed brand identical to the reference listed Nicorette Mint Lozenge in the US].

As part of the product development, Study NICTDP1076 was performed to test whether NSL 2 mg nicotine, with a low level of buffer capacity, (NSL2L) and NSL 4 mg nicotine, with a medium level of buffer capacity, (NSL4M) were bioequivalent with NiQuitinTM lozenge 2 and 4 mg, respectively. NSL2L and NSL4M were of (b)(4) and coated. (b)(4) of exploratory scale, NSL4L (NSL 4 mg nicotine, with a *low* level of buffer capacity) and NSL4H (NSL 4 mg nicotine, with a *high* level of buffer capacity), were included in the study to gain more understanding on buffer level effect on the nicotine exposure.

Table 13 Treatments Study NICTDP1076

Treatment	Drug	Nicotine lozenge dose mg
A	NSL2L [redacted] coated	2
B	NiQuitin lozenge	2
C	NSL4M [redacted] coated	4
D	NiQuitin lozenge	4
E	NSL4L uncoated prototype	4
F	NSL4H uncoated prototype	4

Nicorette Coated Ice Mint Lozenges have been referred to as Nicotine Strongmint Lozenge (NSL) in this study;
NSL4M=Nicotine Strongmint Lozenge 4mg, where M=medium level of buffer capacity; H=high level of buffer capacity; L=low level of buffer capacity;
NSL2L=Nicotine Strongmint Lozenge 2 mg, where L=low level of buffer capacity.
Source: CSR NICTDP1076, Table 2

Subjects were instructed to place the lozenge in their mouth, to occasionally move it from side to side until complete dissolution, and to not chew or swallow the lozenges. Talking was not allowed during the dissolution time. Each subject abstained from any nicotine-containing products for 12 hours before each study treatment, a minimum 10-hour overnight fast including an overnight stay at the clinic. All subjects continued to fast and refrained from lying down during the first 4 hours after dosing. The washout period between treatments was at least 36 hours.

Note on food intake:
Subjects were requested to have breakfast at home before coming to the trial site. Meals during treatment visits were provided at the trial site. Subjects did not eat or drink from 15 min before until 60 min after the start of drug administration. Subjects abstained from alcohol from 24 hours before and throughout each treatment visit. See discussion above?

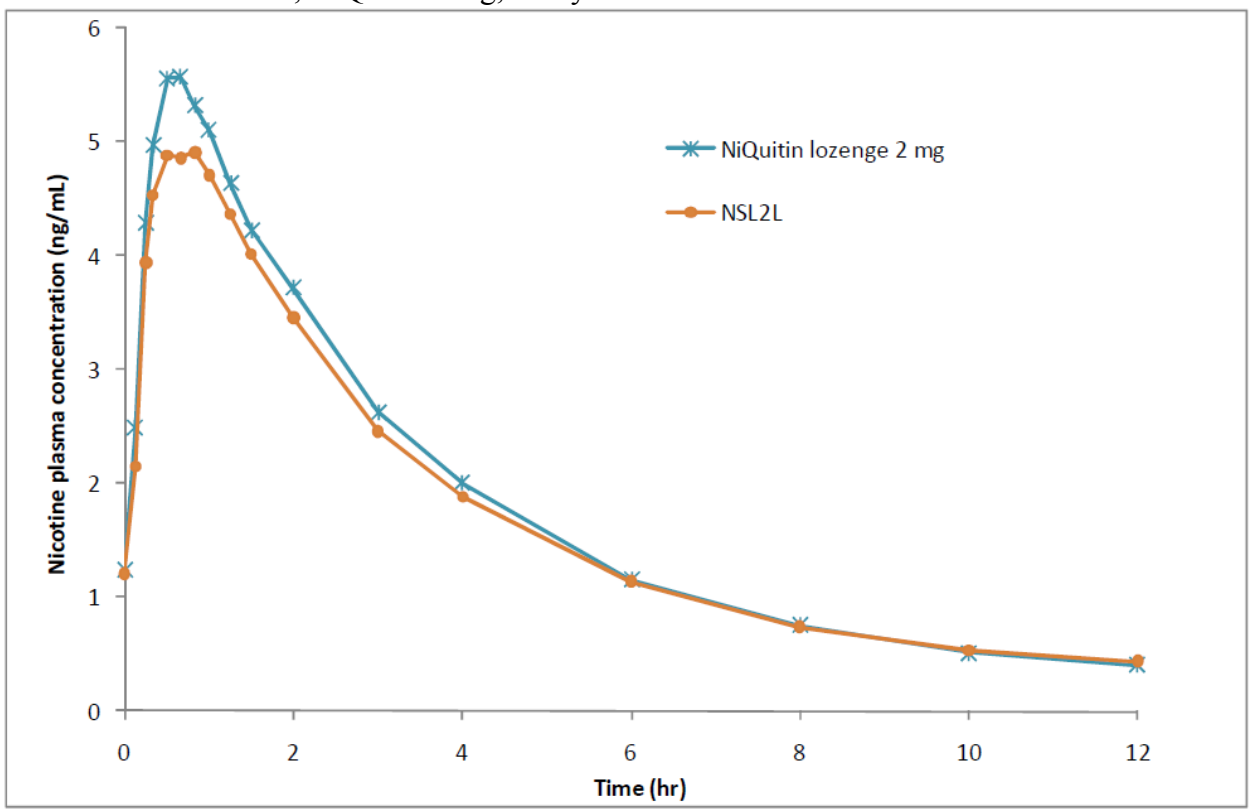
Blood samples were taken at pre-dose, 7.5, 15, 20, 30, 40, 50, 60 min, 1.25, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours post dose. The dissolution time for treatments were collected. Blood samples were [redacted]. Plasma was transferred into screw-capped polypropylene tubes, [redacted] and [redacted] until analysis. Samples were analyzed at the [redacted]. Nicotine in plasma was analyzed using a [redacted] of nicotine, followed by capillary gas chromatography and chemical-ionization mass spectrometry (validated between [redacted]; Lower Limit of Quantification (LLOQ) of 0.5 ng/mL).

For pharmacokinetic analysis, nicotine Cmax and AUC values were corrected for nicotine baseline concentrations, e.g., cCmax, cAUCinf, etc., for each subject using the subject's pre-dose concentration (C_0). Data from treatment visits with baseline nicotine concentrations exceeding 5 ng/mL were excluded (15 subjects) from the analysis.

2 mg dose comparison

The mean nicotine plasma concentration profiles for Treatments A and B plotted over 12 hours are presented in Figure 2.

Figure 2 Mean Nicotine Plasma Concentration vs. Time Profiles over 12 hours for Nicorette Coated Ice Mint Lozenges [referred to as Nicorette Strongmint Lozenge (NSL) 2 mg in this study] and Reference Product, NiQuitin 2 mg, Study NICTDP1076



Test Products: NSL2L=Nicotine Strongmint Lozenge 2 mg, where L=low level of buffer capacity. Nicorette Coated Ice Mint Lozenges have been referred to as Nicotine Strongmint Lozenge (NSL) in this study;
Reference Product: NiQuitin 2 mg.
Source: CSR NICTDP1076 Figure 1

Nicotine 2 mg baseline corrected-arithmetic means [(standard deviation (SD)] of 'cCmax', 'cAUCt' and 'cAUCinf' pharmacokinetic parameters are presented with in Table 14.

Table 14 Mean Arithmetic [(standard deviation (SD)] Nicotine Single Dose, NSL2L, Baseline-corrected Pharmacokinetic Parameters, Study NICTDP1076

Treatment	**n**	**cCmax (ng/mL)**	**tmax* (min)**	**cAUCt (ng/mLxh)**	**cAUC∞ (ng/mLxh)**	**t1/2 (h)**
NSL2L	94	4.9 (1.7)	40	13.7 (7.0)	16.0 (8.6)	3.1
NiQuitin^{TM} lozenge 2	96	5.4 (1.9)	30	14.9 (6.4)	16.9 (7.0)	2.9

Source: CSR NICTDP1076 Table 14.2.2; * Median

Statistical analysis (mean ratio and 90% confidence intervals) of the log-transformed plasma PK parameters of nicotine 2 mg is presented in Table 15.

Table 15 Pharmacokinetic Parameters Estimated Ratios of Geometric Means Nicotine Single Dose 2 mg, NSL2L, Study NICTDP1076

	NSL2L/ NiQuitin™ lozenge 2 mg (n=94-96)	
	Ratio	Interval
cC_{max}	89.3%	84.2-94.8%
$cAUC_t$	90.5%	86.1-95.2%
cAUC□	92.1%	87.7-96.6%

Source: CSR NICTDP1076 Table 14.2.2

Table 16 provides subjects' complete dissolution times of the 2-mg tablet in the mouth.

Table 16 Dissolution Times (minutes) Of The Nicotine Single Dose 2 mg, NSL2L, Study NICTDP1076

Treatment	**n**	**Mean (SD)**	**Min – Max**
NSL2L	94	16.8 (5.5)	7 – 37
NiQuitin™ lozenge 2 mg	96	24.6 (11.2)	11 – 68

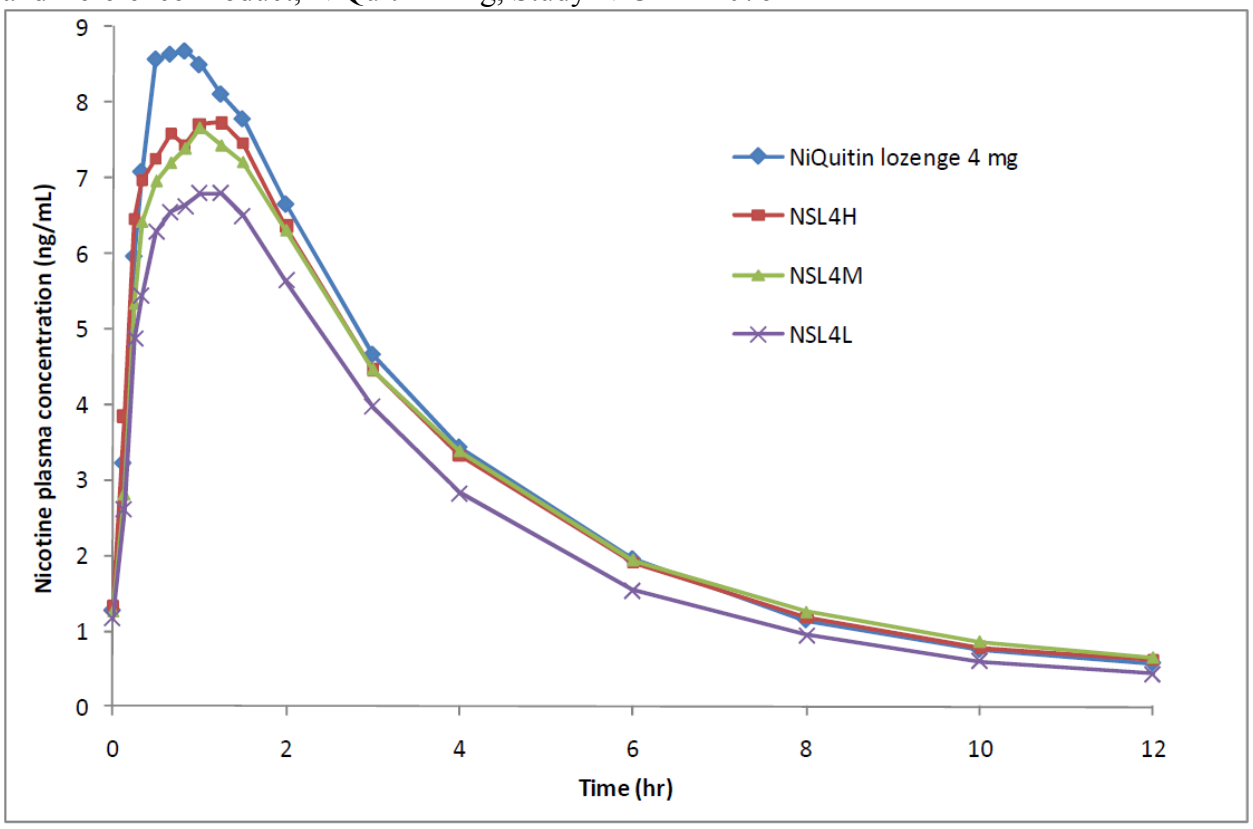
Source: Table 14.2.6

The bioequivalence analysis results indicated that Nicorette Strongmint Lozenge (NSL) 2 mg low level of buffer capacity formulation, NSL2L, and reference product, NiQuitin 2 mg, were bioequivalent.

4 mg dose comparison

The mean nicotine plasma concentration profiles for Treatments C, D, E, and F plotted over 12 hours are presented in Figure 3.

Figure 3 Mean Nicotine Plasma Concentration vs. Time Profiles over 12 hours for Nicorette Coated Ice Mint Lozenges [referred to as Nicorette Strongmint Lozenge (NSL) 4 mg in this study] and Reference Product, NiQuitin 4 mg, Study NICTDP1076



Test Products: NSL4M=Nicotine Strongmint Lozenge 4mg, where M=medium level of buffer capacity; H=high level of buffer capacity; L=low level of buffer capacity; Nicorette Coated Ice Mint Lozenges have been referred to as Nicotine Strongmint Lozenge (NSL) in this study.
Reference Product: NiQuitin 4mg.
Source: CSR NICTDP1076 Figure 2

Nicotine 4 mg baseline corrected-arithmetic means [(standard deviation (SD)] of 'cCmax', 'cAUCt' and 'cAUCinf' pharmacokinetic parameters are presented with in Table 17.

Table 17 Mean Arithmetic [(standard deviation (SD)] Nicotine single dose, NSL 4 mg, Baseline-corrected Pharmacokinetic Parameters, Study NICTDP1076

Treatment	**n**	**cCmax (ng/mL)**	**tmax* (min)**	**cAUCt (ng/mLxh)**	**cAUC∞ (ng/mLxh)**	**t1/2 (h)**
NSL4L	46	7.3 (2.7)	50	23.5 (9.7)	25.7 (10.0)	2.8
NSL4M	97	8.1 (3.4)	50	27.6 (16.8)	30.8 (20.5)	3.1
NSL4H	50	8.6 (3.4)	40	27.6 (14.0)	30.6 (16.9)	3.0
NiQuitin™ lozenge 4 mg	99	9.3 (2.8)	40	29.3 (11.6)	32.0 (13.6)	3.0

Source: CSR NICTDP1076 Table 14.2.2; * Median

Statistical analysis (mean ratio and 90% confidence intervals) of the log-transformed plasma PK parameters of nicotine 4 mg is presented in Table 18.

Table 18 Pharmacokinetic Parameters Estimated Ratios of Geometric Means, Nicotine Single Dose, 4 mg, NSL4L, NSL4M and NSL4H Products, Study NICTDP1076

	NSL4L/ NiQuitin™ lozenge 4 mg (n=46)		**NSL4M/ NiQuitin™ lozenge 4 mg (n=97-99)**		**NSL4H/ NiQuitin™ lozenge 4 mg (n=50)**	
	Ratio	**Interval**	**Ratio**	**Interval**	**Ratio**	**Interval**
cC_{max}	78.5%	71.5-86.2%	85.5%	81.0-90.4%	90.8%	82.9-99.4%
$cAUC_t$	80.5%	72.8-89.0%	88.1%	83.9-92.4%	90.6%	82.1-99.9%
$cAUC_\infty$	80.6%	72.3-90.0%	88.7%	84.7-92.9%	93.3%	83.9-103.8%

Source: CSR NICTDP1076 Table 14.2.2

Table 19 provides subjects' complete dissolution times of the 4 mg tablet in the mouth.

Table 19 Dissolution Times (minutes) Of The Nicotine Single Dose, 4 mg, NSL4L, NSL4M and NSL4H Products, Study NICTDP1076

Treatment	**n**	**Mean**	**Min – Max**
NSL4L	46	16.1 (6.6)	8 – 42
NSL4M	97	17.5 (7.5)	7 – 51
NSL4H	50	15.9 (7.2)	8 – 52
NiQuitin™ lozenge 4 mg	99	26.3 (12.0)	11 – 84

Source: Table 14.2.6

The bioequivalence analysis results indicated that Nicorette Strongmint Lozenge (NSL) 4 mg medium level of buffer capacity and high level of buffer capacity formulations, NSL4M and NSL4H, respectively, and reference product, NiQuitin 4 mg, were bioequivalent. Nicorette Strongmint Lozenge (NSL) 4 mg low level of buffer capacity, NSL4L was not bioequivalent to NiQuitin 4 mg.

3.2.3 What are the characteristics of the dose-systemic exposure relationships for safety?

No formal PK/PD studies were conducted in this NDA to establish the relationship between exposure and safety.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Reviewer comment: The results from the bioanalytical assays are acceptable.

Study CO-160518135743-SCCT

Nicotine concentrations has been determined using a validated method (b)(4) capillary gas chromatography coupled with positive chemical ionization mass spectrometry. The plasma samples (b)(4) (b)(4), where the analytical work was performed. Bioanalytical performances are presented in the following tables (Tables 1 – 3).

Table 1 Summary of the Study Performance

Parameter	**Nicotine**
Calibrated range	(b)(4) ng/ml
Defined LLOQ	0.5 ng/ml
Inter assay precision (CV%) at lowest QC level	5.3
Inter assay accuracy (Bias %) at lowest QC level	2.7
Linearity (mean r^2 of the standard curves)	0.998

(Source: study report co-160518135743; p.348/998)

Table 2 Calibration Standard curves

Date	System	Protocol No.	CAL1 (ng/ml)	CAL2 (ng/ml)	CAL3 (ng/ml)	CAL4 (ng/ml)	CAL5 (ng/ml)	CAL6 (ng/ml) (b)(4)	r^2
n			231	231	232	233	234	234	117
Mean			0.5	1.0	3.2	5.1	7.7	10.4	0.998
sd			0.0	0.0	0.1	0.2	0.2	0.3	0.001
CV%			6.0	4.9	3.7	3.6	2.8	2.7	0.1
Bias%			4.3	-2.1	-1.6	-2.1	0.2	1.4	NA

(Source: study report co-160518135743; p.361-362/998)

Table 3 Quality control samples

Date	System	Protocol No.	QC1 (ng/ml) (b)(4)	Flag	QC2 (ng/ml) (b)(4)	Flag	QC3 (ng/ml) (b)(4)	Flag
n			234		234		234	
Mean			1.6		3.9		8.7	
sd			0.1		0.2		0.5	
CV%			5.3		4.5		5.2	
Bias%			2.7		6.6		4.6	

(Source: study report co-160518135743; p.363-367/998)

Study NICTDP1076

Nicotine concentrations have been determined using a validated [redacted] capillary gas chromatography. Bioanalytical performances are presented in the following tables (Tables 4 – 6).

Table 4 Summary of the Study Performance

Parameter	Nicotine
Calibrated range	[redacted] /ml
Defined LLOQ	0.5 ng/ml
Inter assay precision (CV%) at lowest QC level	9.1
Inter assay accuracy (Bias %) at lowest QC level	-1.6
Linearity (mean r2 of the standard curves)	0.998

(Source: Clinical Study Report NICTDP1076; p.251/1119)

Table 5 Calibration Standard Samples

Date	System	CAL1 (ng/ml)	CAL2 (ng/ml)	CAL3 (ng/ml)	CAL4 (ng/ml)	CAL5 (ng/ml)	CAL6 (ng/ml) [redacted]	R2
n		172	171	177	184	180	178	92
Mean		0.5	1.0	5.4	11.3	35.6	47.6	0.996
sd		0.0	0.1	0.3	0.5	1.4	2.0	0.0
CV%		9.4	7.9	5.0	4.6	3.3	4.2	0.1
Bias%		5.9	2.1	-6.2	-4.0	0.9	1.2	

(Source: Clinical Study Report NICTDP1076; p.262/1119)

Table 6 Quality Control Samples

Date	System	QC1 (ng/ml)	QC2 (ng/ml)	QC3 (ng/ml) [redacted]
n		184.0	183.0	184.0
Mean		1.5	23.1	42.3
sd		0.1	1.5	2.7
CV%		9.1	6.6	6.4
Bias%		-1.6	4.4	7.6

(Source: Clinical Study Report NICTDP1076; p.268/1119)

4.2 Clinical PK and/or PD Assessments

4.2.1 Study CO-160518135743-SCCT

Title: A SINGLE-DOSE, TWO-PERIOD CROSSOVER, RANDOMIZED, FASTING, OPEN-LABEL, BIOEQUIVALENCE STUDY BETWEEN TWO COMMERCIALLY AVAILABLE NRT PRODUCTS IN ADULT HEALTHY SMOKERS (Report Date: 11/27/17)

Reviewer comments: *There are no issues identified with the Applicant's synopsis report.*

The following synopsis was provided by the Applicant.:

INVESTIGATORS: (b)(4)
STUDY CENTERS:
Site 1001: (b)(4) Sweden.
Site 1002: (b)(4) Sweden
PUBLICATIONS (REFERENCE): None.
STUDY INITIATION AND COMPLETION DATES: 02 Mar 2017 to 08 Jun 2017
PHASE OF DEVELOPMENT: Phase 1
STUDY OBJECTIVES
The primary objective of this study was to demonstrate bioequivalence between Nicorette Peppermint lozenge 4 mg (NPL 4 mg) manufactured (b)(4) Nicorette Mint lozenge 4 mg (NML 4 mg) manufactured by GlaxoSmithKline (GSK), USA with respect to single-dose pharmacokinetics of nicotine.
The secondary objectives were:
to further describe the nicotine single-dose pharmacokinetics of the investigational products, to assess the time until complete dissolution of each treatment´s lozenge in the mouth, and
to evaluate the tolerability of the treatments in terms of spontaneously reported and observed Adverse Events (AEs).

METHODOLOGY
STUDY DESIGN
This was a single-dose, two-period crossover, randomized, fasting, open-label, bioequivalence study planned for 230 healthy male and female volunteers, aged between 19 and 55 years, inclusive. The study was conducted at two clinical sites (entitled site 1001 and site 1002).
Single dose of NPL 4 mg (i.e. test product) and NML 4 mg (i.e. reference product) was administered in a standardized mode, on two separate treatment visits. A washout period of at least 36 hours separated the treatment administrations.
An abstinence period of 12 hours including an overnight stay at the clinic was required at both treatment occasions.

Blood for pharmacokinetic analyses was drawn pre-dose (i.e. within 5 minutes before drug administration) and at 3, 5, 10, 15, 20, 30, 40, 50, and 60 minutes, as well as, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after start of drug administration. Thus, 18 samples were collected per treatment visit. Registration of dissolution time was done. Subjects were monitored throughout the study period to capture any AEs that did occur.

NUMBER OF SUBJECTS (PLANNED AND ANALYZED)
Two-hundred thirty (230) subjects were planned and 227 subjects, 100 males and 127 females, were randomized to treatment. In this study, 226 subjects had at least some valid PK data and were therefore included in the full analysis set. Two-hundred eleven (211) of these had evaluable cCmax and cAUCt values for both treatments and were therefore included in the bioequivalence assessment.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION
Healthy male and female subjects between the ages of 19 and 55 years, inclusive, were enrolled. The subjects had to have a Body Mass Index (BMI) between 18.5 and 30 kg/m2. Subjects were to be smokers of at least 10 cigarettes per day and were to have do so for at least one year preceding inclusion. Females had to be in a postmenopausal state or in a premenopausal/perimenopausal state with an effective means of contraception. Males had to have no pregnant or lactating spouse or partner at screening and willingness to utilize an acceptable form of birth control with spouse or any potential partner during the study and for 30 days thereafter.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER
Table S1 provides information about the investigational products.

Table S1: Investigational Products and Identity

	Treatment A (NPL 4 mg)	**Treatment B (NML 4 mg)**
Compound Name	Nicotine	Nicotine
Product Name	Nicorette Peppermint	Nicorette Mint
Dosage Form	Lozenge	Lozenge
Unit Dose	4 mg	4 mg
Route of Administration	Oromucosal	Oromucosal
Manufacturer	(b)(4)	GlaxoSmithKline, Aiken, USA
Batch Number	TK805A	Lot Number 15169 including batch number: A739PP100, A739PP101, A739PP102, A739PP103, A739PP104 and A739PR001
Expiry Date	Sept, 2018	Oct 31, 2017

Subjects were instructed to place the lozenge in their mouth, to occasionally move it from side to side until complete dissolution, and to not chew or swallow the lozenges. Talking was not allowed during the dissolution time.

DURATION OF TREATMENT
Each of the five treatments were given on separate days, which were separated by washout periods without NRT, lasting for at least 36 hours.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: N/A

CRITERIA FOR EVALUATION

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations

All randomized subjects with any valid pharmacokinetic parameter data from at least one of the two investigational products and without protocol deviations having an impact on the nicotine pharmacokinetics, were included in the statistical evaluation.

Safety Evaluations

All subjects that received any treatment were included in the safety analysis.

STATISTICAL METHODS

For all pharmacokinetic parameters, descriptive summary measures were presented by treatment. The pharmacokinetic parameters were summarized based on both the original, uncorrected values as well as corrected values. For continuous variables, statistical summaries were presented. In addition, geometric mean values and coefficients of variation were calculated for cCmax, cAUCt and cAUC□. For tmax, the frequency distribution was additionally tabulated by treatment. In the statistical model-fitting process, for each of the pharmacokinetic parameters, cCmax, cAUCt and cAUC□, only data from subjects with valid parameter values for both compared treatments were included. Statistical comparisons of NPL 4 mg and NML 4 mg with respect to these pharmacokinetic endpoints, were in each case based on a linear model for log transformed (natural log) pharmacokinetic parameter data. In each case an interval estimate with confidence level 90% for the log-scale treatment mean difference was calculated from the fitted model. The calculated interval was then back transformed to the original measurement scale to obtain a 90% confidence interval for the ratio of geometric means. All AEs reported during the AE reporting period were listed by subject ID and last treatment administered before the AE. Any SAE was listed separately. The number and percentage of subjects experiencing AEs were tabulated by treatment, system organ class, and preferred term. In addition, number and percentage of subjects' experienced AEs with a possible, probable, or very likely relation the investigational product were separately tabulated by treatment, system organ class, preferred term, and worst recorded severity. Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 was used as AE classification system

RESULTS

SUBJECT DISPOSITION AND DEMOGRAPHY

The number of subjects included in the assessment are displayed in Table S2.

Table S2: Evaluable Subjects

Treatment	**PK**
NPL 4 mg	217
NML 4 mg	220

All randomized subjects were analyzed with respect to safety information in this study. Two-hundred twenty-seven (227) subjects, 100 males and 127 females, were included in the study. Two-hundred twenty-one (221) were White, 3 were Black or African American and 3 were Other. Their average age was 30.0 years (range 19-54 years) and their average BMI was 23.9 kg/m2 (range 18.8-29.7 kg/m2). The subjects were smokers consuming on average 15.5 cigarettes per

day (range 10-30 cigarettes) and they had been smokers for 12.8 years on average (range 1-40 years). Thus, age, BMI and smoking habits were in accordance with the inclusion criteria.
All subjects were healthy adult volunteers. None of the subjects had conditions or a medical history that the investigator considered sufficient to affect the conduct of the study or to represent a potential risk to the subject during study participation.

PHARMACOKINETIC, PHARMACODYNAMIC, AND/OR OTHER RESULTS
Pharmacokinetic
Figure S1 displays the average plasma concentration profiles of nicotine for the study treatments, plotted over 12 hours after start of administration. Observed geometric means of cCmax, cAUCt and cAUCinf are displayed in Table S3. Model-based estimates and corresponding 90% confidence intervals for the ratios of the population geometric means of the pharmacokinetic parameters between the NPL 4 mg and NML 4 mg are presented in Table S4.

Figure S1: Mean Nicotine Plasma Concentration vs. Time Profiles over 12 hours after Start of Administration

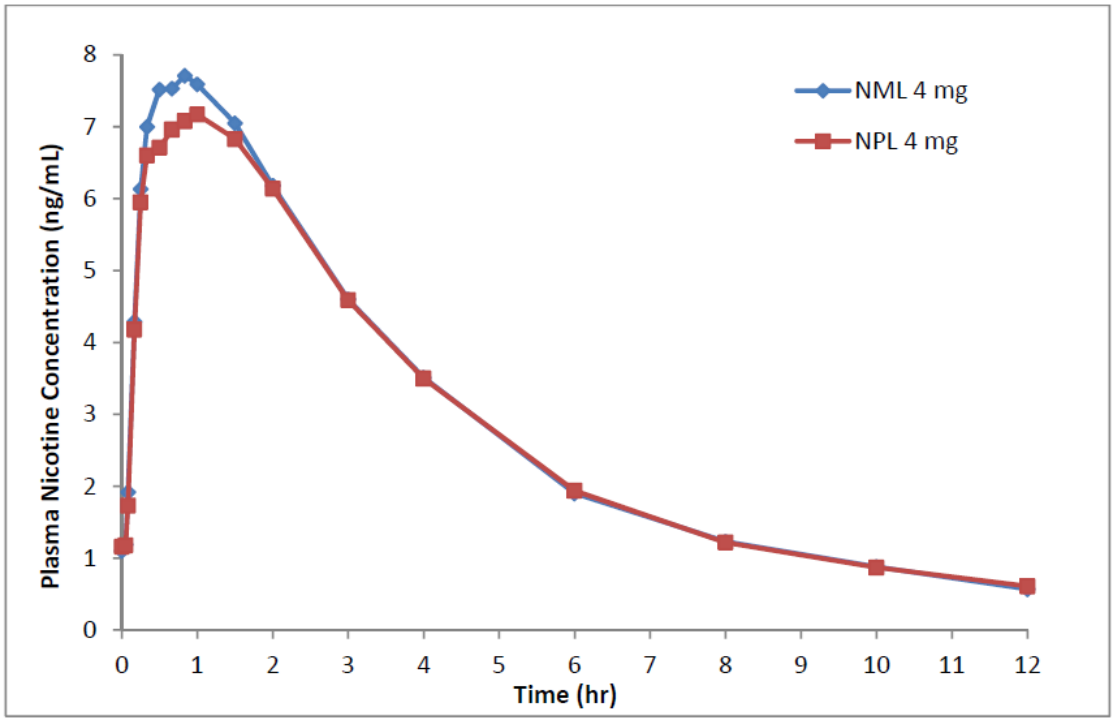


Table S3: Pharmacokinetic Parameters Observed Geometric Means (CV%)

PK parameter	**NML 4 mg** (n=220)	**NPL 4 mg** (n=217)
cC_{max} (ng/mL)	7.80 (41.67)	7.47 (39.87)
$cAUC_t$ (ng/mLxhr)	26.82 (42.71)	25.94 (42.62)
$cAUC_{inf}$ (ng/mLxhr)	29.49 (43.07)	28.52 (42.66)

Table S4: Pharmacokinetic Parameters Estimated Ratios of Geometric Means

	NPL 4 mg vs. NML 4 mg (n=211)	
	Ratio (%)	**90% CI (%)**
cC_{max}	94.9	91.9 – 98.1
$cAUC_t$	95.6	93.2 – 98.0
$cAUC_{inf}$	95.6	93.3 – 97.9

Table S5 provide across-subject averages and standard deviations for times until complete dissolution of the tablets in the mouth.

Table S5: Dissolution Time

	Mean	**SD**	**Median**	**Min**	**Max**
NML 4 mg	19.80	11.39	17.0	5	107
NPL 4 mg	12.92	5.88	12.0	3	44

NML: N=221; NPL N=218

SAFETY RESULTS

In total, 314 treatment-emergent AEs were reported. Two-hundred thirty-four (234) of these were considered to be "possibly", "probably" or "very likely" related to treatment Table S6. Of the 234 AEs 203 were considered "mild" in severity, 28 "moderate" and 3 "severe". No subject withdrew from the study due to AE after the first treatment. One non-treatment related SAE was reported in this study. No deaths, pregnancies or other significant AEs were reported. Sixty-four (64) subjects experienced at least one AE possibly, probably or very likely related to treatment with NML 4 mg. The corresponding numbers with NPL 4 mg was 81. Gastrointestinal Disorders represented the most commonly reported AEs, followed by Respiratory, Thoracic. In general, AEs were consistent with current understanding of the safety profile for nicotine lozenges.

Table S6: Summary of Number of Subjects with Adverse Events Possibly, Probably or Very Likely Related to Treatment

System Organ Class	Adverse Event (Preferred Term)	NML 4 mg (n=225)	NPL 4 mg (n=221)
Cardiac disorders	Palpitations	1	- 1
	Tachycardia	-	
Ear and labyrinth disorders	Vertigo	8	9
Eye disorders	Dry eye	1	-
Gastrointestinal disorders	Abdominal pain upper	1	3
	Dry mouth	1	- 11
	Dyspepsia	8	1
	Dysphagia	- 1	- 1
	Eructation	1	36
	Flatulence	24	1
	Nausea	-	4
	Oral discomfort Salivary	-	1
	hypersecretion	- 1	1
	Stomatitis		
	Vomiting		
General disorders and administration site conditions	Chest discomfort	3	1
	Chest pain	1	- 1
	Fatigue	-	
Nervous system disorders	Headache	11	12
	Migraine	1	-
	Somnolence	2	-
Respiratory, thoracic and mediastinal disorders	Cough	-	3
	Dysphonia	- 5	1
	Hiccups		13
	Increased upper airway secretion	1	-
	Rhinorrhoea	-	1
	Throat irritation	20	25
	Throat tightness	4	5
Skin and subcutaneous tissue disorders	Cold sweat	3	5

Note: Nicorette Coated Ice Mint Lozenge 4 mg, known also as Nicorette Peppermint Lozenge (NPL); Nicorette Original/Mint Lozenge (NML)

CONCLUSIONS

 Bioequivalence was demonstrated between Nicorette Peppermint lozenge 4 mg and Nicorette Mint lozenge 4 mg.

 On average, the Nicorette Mint lozenge 4 mg dissolved in about 20 minutes. Nicorette Peppermint lozenge 4 mg dissolved in about 13 minutes.

 Overall the AE data was consistent with the existing knowledge of the safety profile of NRT products.

Additional information pertinent from the main study report:

Inclusion Criteria:

Each subject met all of the following inclusion criteria (and none of the exclusion criteria) to be eligible for enrollment into the study:

1. Healthy male and/or female subjects between the ages of 19 to 55 years, inclusive. Healthy was defined as the absence of clinically relevant abnormalities as judged by the investigator on the basis of a detailed medical history, physical examination, blood pressure and heart rate measurements, 12-lead electrocardiogram (ECG), as well as clinical laboratory tests. The responsible investigator may have requested additional investigations or analyses if necessary.
2. Smoked at least 10 tobacco cigarettes daily for at least one year preceding inclusion.
3. Subjects would have a Body Mass Index (BMI) between 18.5 to 30 kg/m2, inclusive, and a body weight >50 kg.
4. For females: Postmenopausal state (absence of menstrual discharge for at least two years and a serum FSH level exceeding 30 IU/L) or premenopausal /perimenopausal state with an effective means of contraception (as defined in 9.3.4) during the study and 30 days thereafter.
For males: No pregnant or lactating spouse or partner at screening and willingness to utilize an acceptable form of birth control with spouse or any potential partner during the study and for 30 days thereafter.
5. Had a personally signed and dated informed consent document before participating in any study-specific procedures, indicating that the subject had been informed of all pertinent aspects of the study.
6. Was able to comprehend the requirements of the study (based upon clinical site personnel's assessment), and was willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures specified in the protocol.

Exclusion Criteria:

A subject who met any of the following exclusion criteria was not included in the study:

1. Regularly used medications other than contraceptives as specified in Inclusion criteria no 4. Vitamins, dietary, and herbal supplements had to be discontinued at least 7 days before the first dose of study medication.
2. Subjects who did not abstain from using nicotine-containing products (beside treatments specified in this protocol) and smoking from 12 hours before planned treatment administration and throughout each treatment visit.
3. Was hypersensitive, intolerant, or experienced an allergic reaction to the active ingredient(s) or excipients of drug products that were used in the study.
4. Females with a positive pregnancy test and/or were breast-feeding.

5. Had a positive test for human immunodeficiency virus (HIV) 1 and 2 antibodies, hepatitis B surface antigen (HBsAg), or hepatitis C antibodies (anti-HCV).
6. History of alcoholism or substance abuse, as judged by the Investigator, within the past 2 years of screening.
7. Treatment with an investigational drug within 3 months preceding the first dose of study treatment.
8. Donation or loss of blood within 3 months prior to the first treatment visit if the estimated lost blood volume equaled or exceeded 450 mL.
9. Preplanned surgery or procedures during the study period, if this may interfere with the conduct of the study.
10. Relationship to persons involved directly with the conduct of the study (i.e., principal investigator; sub investigators; study coordinators; other study personnel; employees or contractors of the Sponsor or Johnson & Johnson subsidiaries; and the families of each).
11. Abnormal oral mucosa including ulcerations which could deteriorate by the use of nicotine lozenges.

Treatments Administered:
Following a monitored 12-hour nicotine abstinence period (including monitored fasting), subjects received the first study treatment in the morning of the treatment days. NPL 4 mg (test product) and NML 4 mg (reference product) were both oromucosal formulations which were placed in the mouth. Subjects were instructed to place the lozenge in their mouth, to occasionally move it from side to side until complete dissolution, and to not chew or swallow the lozenges. Talking was not allowed during the dissolution time.

Selection and Timing of Dose for Each Subject:
Each subject abstained from any nicotine-containing products for 12 hours before each study treatment. Following a minimum 10-hour overnight fast, an oral dose of the assigned formulation was administered in the morning to subjects according to the randomization scheme. Study medications were administered to each subject for the purpose of accurate sampling time. In order to standardize the conditions, all subjects continued to fast and refrained from lying down during the first four hours after dosing.

Meals and Dietary Restrictions:
 Subjects received a snack in the evening of admission followed by an overnight fast for at least 10 hours prior to treatment drug administration.
 Water was provided *ad libitum* until 1-hour pre-dose and beginning again when the lozenge was completely dissolved, but not earlier than 1 hour after the administration of the drug.
 Fasting continued for at least 4 hours following start of drug administration.
 Meals during treatment visits were standardized (i.e. same at each visit per subject) and provided by the study site.
 Lunch, snack, and dinner was provided approximately 4, 7.5, and 10 hours after the start of drug administration.

Alcohol and tobacco:
 Subjects abstained from alcohol from 24 hours before and throughout each visit (i.e. after signing informed consent and throughout the study period).

□ Subjects abstained from using any nicotine-containing products (beside treatments specified in this protocol) and smoking from 12 hours before planned treatment administration and throughout each treatment visit.

Prior and Concomitant Therapy:
Any medications, prescription and nonprescription drugs taken within 14 days prior to the screening visit and to the first dose of study drug were documented as a prior medication. Medications taken after the first dose of study drug until after discharge from the study were documented as concomitant medications. Occasional use of paracetamol, NSAID, nasal spray including local steroids and antihistamines was allowed during the study period but should have been approved by the Investigator and recorded in the CRF.

The investigator should approve medication that may be required due to *unexpected illness* during the study. The usage was reported to the Sponsor and recorded on the case report forms. Subjects abstained from using prescription or nonprescription drugs, vitamins, and dietary supplements in accordance with the inclusion/exclusion criteria. Vitamins, dietary, and herbal supplements were discontinued at least 7 days before the first dose of study medication. Subjects abstained from using any nicotine-containing products (beside treatments specified in this protocol) and smoking from 12 hours before planned treatment administration and throughout each treatment visit. All concomitant medication taken during the study was recorded with indication, daily dose, and, if available, start and stop times and dates of administration. All subjects were questioned about concomitant medication at each clinic visit.

Pharmacokinetic Sampling and Analytical Methodology:
Blood Plasma for Analysis of Nicotine:
It was a Sponsor requirement that the study was conducted in a nicotine free environment, which also included that the staff involved during the study period were prohibited to use any kind of nicotine products that could contaminate the samples. During each treatment visit, 2.6 mL blood samples for pharmacokinetic analysis were collected into appropriately labeled tubes containing lithium heparin. The blood and plasma tubes were labeled with the following information (at a minimum): subject randomization number, sampling time, treatment visit number, protocol number, and any applicable site specific sample identification code. Blood samples were collected before dosing (pre-dose) and at specific times following each designated dose. All efforts were made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. Samples obtained more than one (1) minute of nominal time were captured as a protocol deviation and were recorded according to instructions. If the time for drawing a sample was long (i.e. exceeding one (1) minute), the sampling was aborted after one (1) minute. The obtained sample volume, even if very small, was handled as any sample. Samples were centrifuged at approximately (b)(4)

Determination of Nicotine in Plasma Samples:
Nicotine in plasma was analyzed using a validated analytical method in compliance with (b)(4) (b)(4) standard operating procedures. The mass spectrometric method was a GC-MS

method validated according to current guidelines for Bioanalytical method validation. The method was validated between [redacted](b)(4) nicotine/ml blood plasma. The mass spectrometric ionization was chemical ionization [redacted](b)(4) and detection was [redacted](b)(4) with [redacted](b)(4), respectively. In order to eliminate contamination from the environment, the laboratories and its staff were nicotine free. Glassware used in the preparation of calibration standards, quality control samples, sample preparation etc. were all new and washed before use according to the method. Thanks to these precautions and the specificity of the GC-MS method, nicotine responses in blank samples were kept to a minimum, well below the required <20% of Lower Limit of Quantification (LLOQ) (0.5 ng/ml).

Calculation of Pharmacokinetic Parameters:
Individual plasma concentration data from each subject and the corresponding blood sampling times were the basic data for pharmacokinetic analyses. Ordinarily, nominal sampling times were used; however, actual sampling times were used whenever they deviated by more than 1 minute from the nominal times. For subject-level analyses, plasma concentrations below the lower limit of LLOQ and observed before tmax were set to LLOQ/2, whereas concentrations below the LLOQ and observed after tmax were omitted. When calculating descriptive statistics for plasma concentrations across subjects for separate sampling times, all values below LLOQ were set to LLOQ/2. Data from treatment visits with baseline nicotine concentrations exceeding 5 ng/mL were excluded from the pharmacokinetic evaluation. Exclusion of data due to non-compliance with study procedures or other factors that may have influenced the pharmacokinetics of nicotine were evaluated and documented in the study report before the responsible drug analyst(s) and pharmacokineticists were aware of individual subject treatment allocation. The calculations were performed using Phoenix WinNonlin (version 6, Certara). Certara Output was checked against the bioanalytical data. Cmax, AUCt and AUC_∞ was corrected for nicotine baseline concentrations (for each subject) according to the following equations, where C0 was the baseline nicotine concentration:

$cC_{max} = C_{max} - C_0 \cdot e^{-\lambda z \cdot tmax}$

$cAUC_t = cAUC_\infty - ((C_t - C_0 \cdot e^{-\lambda z \cdot t}) / \lambda_Z)$, where t was the last time point with a concentration exceeding LLOQ

$cAUC_\infty = AUC_\infty - C_0/\lambda_Z$

In addition, AUC_{extrap} (the extrapolated part of $cAUC_\infty$) was calculated according to: $AUC_{extrap} = (cAUC_\infty - cAUC_t)/ cAUC_\infty$

Dissolution Time of the lozenge:
Subjects themselves indicated when they felt that the lozenge was completely dissolved. Site personnel then inspected the oral cavity to confirm that the lozenge was dissolved and recorded the time.

Determination of Sample Size:
The primary objective of the study was to demonstrate bioequivalence between NPL 4 mg and NML 4 mg, with respect to single-dose pharmacokinetics of nicotine. In a previous study comparing the single dose pharmacokinetics of NPL 4 mg and NML 4 mg, bioequivalence was demonstrated based on the outcome of n = 103 evaluable subjects [8]. In view of the relatively

large amount of historical data thus available, it seemed reasonable to use the following assumptions based on data from the previous study for the sample size calculations of the performed study. The true treatment geometric mean ratios of cCmax and cAUCt were both expected to belong to the interval (86%, 100%). In addition, the maximum log-scale within-subject standard deviation was assumed to not exceed 0.25. With these assumptions and in each case using a significance level of 5% for tests of the null hypotheses of no bioequivalence for the two primary pharmacokinetic endpoints, cCmax and cAUCt, a balanced crossover study with 104 fully evaluable subjects in each of the two treatment sequence groups had a statistical power of at least 90% to demonstrate bioequivalence between the two treatments. To compensate for an assumed dropout rate of 10%, in total 230 (= 208 + 22) subjects were included in the study.

Descriptive and Summary Statistics of Study Data:
Demographic and other baseline characteristics were summarized in tabular format. For all pharmacokinetic parameters, descriptive summary measures were presented by treatment. The pharmacokinetic parameters were summarized based on both the original, uncorrected values as well as corrected values. Measured plasma nicotine values were summarized by treatment and measurement time point. Descriptive statistics of lozenge dissolution times were tabulated by treatment. For continuous variables, statistical summaries included mean values, standard deviations, medians and maximum as well as minimum values were presented. In addition, geometric mean values and coefficients of variation were calculated for cCmax, cAUCt and $cAUC_{\infty}$. For tmax, the frequency distribution was additionally tabulated by treatment.

Analysis of Pharmacokinetic Parameters:
In the statistical model-fitting process, for each of the pharmacokinetic parameters, cCmax, cAUCt and $cAUC_{\infty}$, only data from subjects with valid parameter values for both compared treatments were included. Statistical comparisons of NPL 4 mg and NML 4 mg with respect to these pharmacokinetic endpoints, were in each case based on a linear model for log transformed (natural log) pharmacokinetic parameter data. The log transformed data was assumed to follow a normal distribution. For each parameter evaluation, the statistical model included covariate adjustments for period, treatment sequence, and subject, nested within sequence, as fixed effects. In addition, the logarithm of the baseline nicotine concentration, log (C0), was included as a covariate in the model. Carry-over effects were assumed ignorable. In each case an interval estimate with confidence level 90% for the log-scale treatment mean difference was calculated from the fitted model. The calculated interval was then back transformed to the original measurement scale to obtain a 90% confidence interval for the ratio of geometric means.

Disposition of Subjects:
Of 304 subjects screened for entry into the study, 227 were randomized to treatment. In total 9 subjects discontinued after randomization at different stages:
- Eight (8) subjects (Subject ID (b)(6), (b)(6)) discontinued prior to the second treatment visit, but after completing the first treatment.
- One (1) subject (Subject ID (b)(6)) withdrew during the second treatment visit (8 hours after start of treatment administration).

Hence, 218 subjects completed both treatments of the study. However, 219 received both doses (as Subject ID (b)(6) withdrew after treatment administration at the second treatment visit).

Data Sets Analyzed:
In this study, 226 subjects had at least some valid pharmacokinetic data and were therefore included in the full analysis set. Eight (8) of the withdrawals described in 10.1 obviously resulted in incomplete PK data for those subjects and treatments. In addition, 4 subjects (Subj ID [redacted] and [redacted]) had baseline plasma nicotine concentration higher that 5 ng/mL for one treatment. One (1) subject (Subject ID [redacted]) had high baseline concentration for both treatments. Corresponding PK data for those subjects and treatments were therefore excluded from statistical evaluations. Two-hundred eleven (211) subjects had evaluable cCmax and cAUCt values for both treatments and were therefore included in the bioequivalence assessment.

Demography and Baseline Characteristics:
Two-hundred twenty-seven (227) subjects, 100 males and 127 females, were included in the study. Two-hundred twenty-one (221) were White, 3 were Black or African American and 3 were Other. Their average age was 30.0 years (range 19-54 years) and their average BMI was 23.9 kg/m2 (range 18.8-29.7 kg/m2). The subjects were smokers consuming on average 15.5 cigarettes per day (range 10-30 cigarettes) and they had been smokers for 12.8 years on average (range 1-40 years). Thus, age, BMI and smoking habits were in accordance with the inclusion criteria. All subjects were healthy adult volunteers. None of the subjects had conditions or a medical history that the investigator considered would affect the conduct of the study or to represent a potential risk to the subject during study participation.

Prior and Concomitant Medications:
One-hundred thirty-one (131) subjects used drugs besides the study medication sometime between 14 days before the screening visit and the end of the last treatment visit. These subjects met the specified protocol requirements regarding the use of concomitant medications. The most frequently used drugs were paracetamol, contraceptives and ibuprofen.

Plasma Pharmacokinetics results:
The distributions of cCmax and cAUCt values are graphically shown in Figure 2 and Figure 3.

Table 10: Pharmacokinetic Parameters Arithmetic Means (SD)

PK parameter	**NML 4 mg** (n=220-221)	**NPL 4 mg** (n=217-218)
cC_{max} (ng/mL)	8.37 (3.49)	7.97 (3.18)
$cAUC_t$ (ng/mLxhr)	28.98 (12.38)	28.06 (11.96)
$cAUC_{inf}$ (ng/mLxhr)	31.79 (13.69)	30.77 (13.13)
$cAUC_{extrap}$ (%)	9.0 (3.2)	9.0 (3.0)
t_{max}* (hr)	0.67 (0.17-2.00)	0.83 (0.17-3.00)
λ_z (hr^{-1})	0.24 (0.06)	0.24 (0.06)
$t_{1/2}$ (hr)	3.11 (0.99)	3.08 (0.82)

Source: Tables 14.2.2.1 and 14.2.2.2; * Median (Min – Max)

Figure 2: Distribution of cCmax by treatment

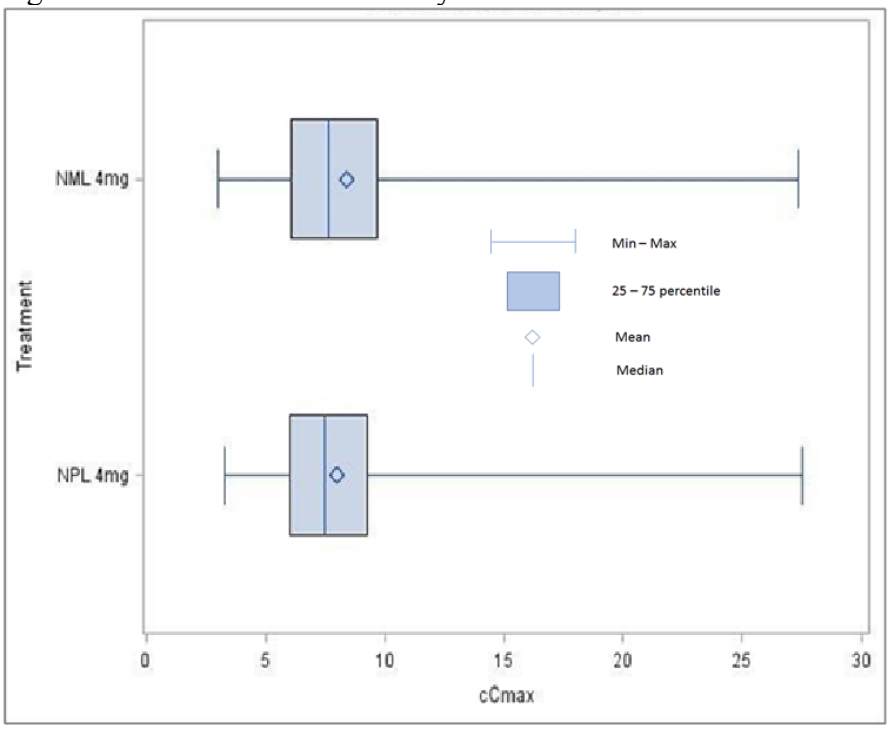
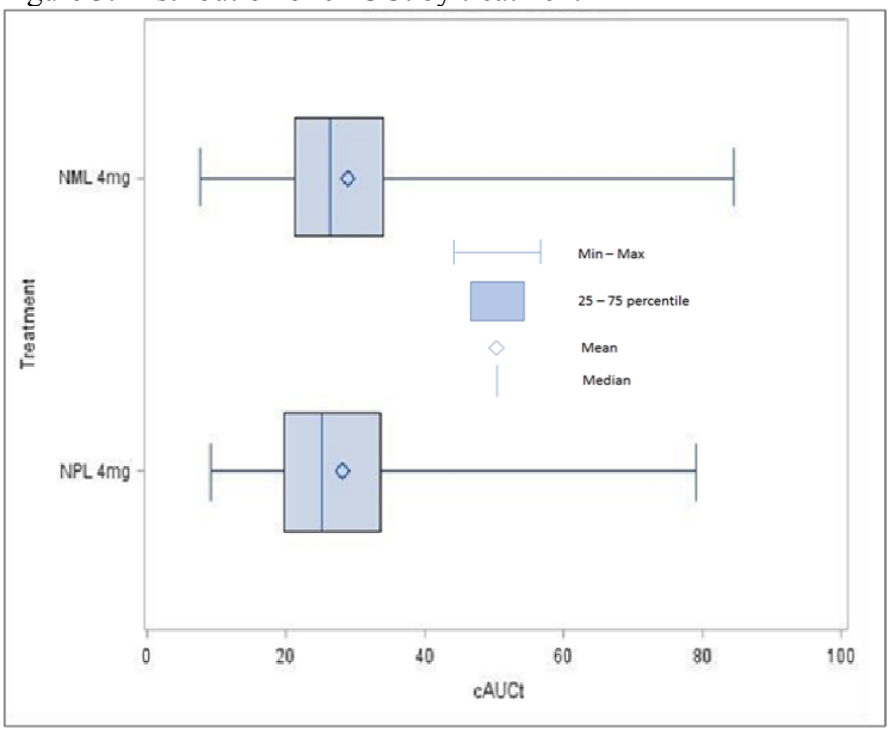


Figure 3: Distribution of cAUCt by treatment



Appendix:

Table 14.1.2.1 Demographics and Baseline Characteristics All randomized subjects

Variable	All randomized subjects (N=227)
Age (years)	
N	227
Mean	30.0
S.D.	9.36
Median	26.0
Min-Max	(19-54)
Race	
WHITE	221(97.4%)
BLACK OR AFRICAN AMERICAN	3(1.3%)
OTHER	3(1.3%)
Total	227(100%)
Sex	
MALE	100(44.1%)
FEMALE	127(55.9%)
Total	227(100%)
Height - males (cm)	
N	100
Mean	181.4
S.D.	6.70
Median	181.0
Min-Max	(163.0-200.0)
Height - females (cm)	
N	127
Mean	167.9
S.D.	6.22
Median	168.0
Min-Max	(155.0-183.0)
Weight - males (kg)	
N	100
Mean	78.5
S.D.	10.40
Median	78.0
Min-Max	(56.8-104.0)
Weight - females (kg)	
N	127
Mean	67.7
S.D.	8.60
Median	66.7
Min-Max	(51.5-87.0)
BMI (kg/m2)	
N	227
Mean	23.9
S.D.	2.81
Median	23.8
Min-Max	(18.8-29.7)
Systolic blood pressure	
N	227
Mean	122.2
S.D.	10.69
Median	121
Min-Max	(98-154)
Diastolic blood pressure	
N	227
Mean	74.0
S.D.	8.91
Median	74
Min-Max	(51-103)
Pulse	
N	227
Mean	72.2
S.D.	10.30
Median	72
Min-Max	(43-100)
Years smoking	
N	227
Mean	12.8
S.D.	9.10
Median	10.0
Min-Max	(1-40)
Cigarettes/day	
N	227
Mean	15.5
S.D.	4.04
Median	15.0
Min-Max	(10-30)

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Uncorrected Pharmacokinetic Parameters Summary Statistics:

Table 14.2.2.1 Uncorrected Pharmacokinetic Parameters Summary Statistics Subjects in Full Analysis Set

Parameter	NML 4mg	NPL 4mg
Cmax (ng/ml)		
N	221	218
Mean	9.35	8.93
Geometric Mean	8.70	8.37
S.D.	3.91	3.46
CV	41.87	38.73
Median	8.80	8.40
Min-Max	(3.2-29.0)	(3.4-27.7)
AUCt (hr*ng/ml)		
N	221	218
Mean	34.08	33.46
Geometric Mean	31.28	30.65
S.D.	15.22	14.86
CV	44.66	44.41
Median	30.60	30.38
Min-Max	(8.2-102.8)	(10.1-96.5)
AUCinf (hr*ng/ml)		
N	220	217
Mean	37.09	36.27
Geometric Mean	34.05	33.32
S.D.	16.99	16.04
CV	45.81	44.23
Median	33.06	33.12
Min-Max	(11.1-118.5)	(11.8-112.9)
Tmax (hr)		
N	221	218
Mean	0.82	0.92
S.D.	0.47	0.60
Median	0.67	0.83
Min-Max	(0.17-2.00)	(0.17-3.00)
Tmax (hr) - Frequency dist.		
0.17	2(<1.0%)	4(1.8%)
0.25	15(6.8%)	26(11.9%)
0.28	1(<1.0%)	0
0.33	28(12.7%)	29(13.3%)
0.50	39(17.6%)	15(6.9%)
0.53	0	1(<1.0%)
0.67	29(13.1%)	23(10.6%)
0.83	31(14.0%)	27(12.4%)
0.88	1(<1.0%)	0
1.00	35(15.8%)	35(16.1%)
1.50	27(12.2%)	31(14.2%)
1.57	0	1(<1.0%)
1.69	0	1(<1.0%)
2.00	13(5.9%)	22(10.1%)
3.00	0	3(1.4%)
Total	221(100%)	218(100%)
Lambda z (1/hr)		
N	220	217
Mean	0.24	0.24
S.D.	0.06	0.06
Median	0.24	0.24
Min-Max	(0.08-0.42)	(0.11-0.46)
Terminal half life (hr)		
N	220	217
Mean	3.11	3.08
S.D.	0.99	0.82
Median	2.92	2.91
Min-Max	(1.65-8.24)	(1.49-6.28)

NML 4mg = Nicorette Mint Lozenge 4 mg
NPL 4mg = Nicorette Peppermint Lozenge 4 mg

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Baseline-corrected Pharmacokinetic Parameters Summary Statistics:

Table 14.2.2.2 Baseline-corrected Pharmacokinetic Parameters Summary Statistics Subjects in Full Analysis Set

Parameter	NML 4mg	NPL 4mg
Cmax* (ng/ml)		
N	220	217
Mean	8.37	7.97
Geometric Mean	7.80	7.47
S.D.	3.49	3.18
CV	41.67	39.87
Median	7.66	7.47
Min-Max	(3.0-27.3)	(3.2-27.5)
AUCt* (hr*ng/ml)		
N	220	217
Mean	28.98	28.06
Geometric Mean	26.82	25.94
S.D.	12.38	11.96
CV	42.71	42.62
Median	26.38	25.23
Min-Max	(7.7-84.6)	(9.2-79.2)
AUCinf* (hr*ng/ml)		
N	220	217
Mean	31.79	30.77
Geometric Mean	29.49	28.52
S.D.	13.69	13.13
CV	43.07	42.66
Median	28.82	27.68
Min-Max	(10.4-97.4)	(11.0-90.1)
Extrapolated area* (%)		
N	220	217
Mean	9.0	9.0
S.D.	3.2	3.0
Median	8.4	8.6
Min-Max	(3.3-26.0)	(2.6-24.3)

*Parameter is corrected for baseline nicotine

NML 4mg = Nicorette Mint Lozenge 4 mg
NPL 4mg = Nicorette Peppermint Lozenge 4 mg

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Subjects with Treatment Emergent Adverse Events By Worst Case Severity:

Table 14.3.1.3 Subjects with Treatment Emergent Adverse Events By System Organ Class, Preferred Term, and Worst Case Severity* Subjects in Safety Analysis Set

14.3.1.3. Subjects with Treatment Emergent Adverse Events By Worst Case Severity

Table 14.3.1.3 (Page 1 of 4)
Subjects with Treatment Emergent Adverse Events
By System Organ Class, Preferred Term, and Worst Case Severity*
Subjects in Safety Analysis Set

System Organ Class Preferred Term Name	NML 4mg (N=225) Mild n (%)	NML 4mg (N=225) Moderate n (%)	NML 4mg (N=225) Severe n (%)	NPL 4mg (N=221) Mild n (%)	NPL 4mg (N=221) Moderate n (%)	NPL 4mg (N=221) Severe n (%)
SUBJECTS WITH AT LEAST ONE AE	69(30.7%)	15(6.7%)	1(<1.0%)	78(35.3%)	19(8.6%)	1(<1.0%)
CARDIAC DISORDERS	1(<1.0%)	0	0	1(<1.0%)	0	0
PALPITATIONS	1(<1.0%)	0	0	0	0	0
TACHYCARDIA	0	0	0	1(<1.0%)	0	0
EAR AND LABYRINTH DISORDERS	8(3.6%)	0	0	9(4.1%)	0	0
VERTIGO	8(3.6%)	0	0	9(4.1%)	0	0
EYE DISORDERS	1(<1.0%)	0	0	2(<1.0%)	0	0
DRY EYE	1(<1.0%)	0	0	0	0	0
EYE IRRITATION	0	0	0	1(<1.0%)	0	0
LACRIMATION INCREASED	0	0	0	1(<1.0%)	0	0
GASTROINTESTINAL DISORDERS	34(15.1%)	4(1.8%)	1(<1.0%)	46(20.8%)	5(2.3%)	1(<1.0%)
ABDOMINAL PAIN UPPER	2(<1.0%)	0	0	3(1.4%)	0	0
CONSTIPATION	0	0	0	1(<1.0%)	0	0
DIARRHOEA	2(<1.0%)	1(<1.0%)	0	1(<1.0%)	0	0
DRY MOUTH	1(<1.0%)	0	0	0	0	0
DYSPEPSIA	8(3.6%)	0	0	9(4.1%)	2(<1.0%)	0
DYSPHAGIA	0	0	0	1(<1.0%)	0	0
ERUCTATION	1(<1.0%)	0	0	0	0	0
FLATULENCE	1(<1.0%)	0	0	1(<1.0%)	0	0
FOOD POISONING	0	0	0	1(<1.0%)	0	0
GASTROINTESTINAL SOUNDS ABNORMAL	0	0	0	1(<1.0%)	0	0
NAUSEA	23(10.2%)	2(<1.0%)	1(<1.0%)	32(14.5%)	4(1.8%)	1(<1.0%)
ORAL DISCOMFORT	0	0	0	1(<1.0%)	0	0
SALIVARY HYPERSECRETION	0	0	0	3(1.4%)	1(<1.0%)	0

* Version is 20.0.

NML 4mg = Nicorette Mint Lozenge 4 mg
NPL 4mg = Nicorette Peppermint Lozenge 4 mg

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System Organ Class Preferred Term Name	NML 4mg (N=225) Mild n (%)	NML 4mg (N=225) Moderate n (%)	NML 4mg (N=225) Severe n (%)	NPL 4mg (N=221) Mild n (%)	NPL 4mg (N=221) Moderate n (%)	NPL 4mg (N=221) Severe n (%)
STOMATITIS	0	0	0	1(<1.0%)	0	0
VOMITING	1(<1.0%)	1(<1.0%)	1(<1.0%)	1(<1.0%)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3(1.3%)	0	0	2(<1.0%)	1(<1.0%)	0
CHEST DISCOMFORT	3(1.3%)	0	0	0	1(<1.0%)	0
CHEST PAIN	1(<1.0%)	0	0	0	0	0
CHILLS	0	0	0	1(<1.0%)	0	0
FATIGUE	0	0	0	1(<1.0%)	0	0
IMMUNE SYSTEM DISORDERS	0	0	0	3(1.4%)	0	0
HYPERSENSITIVITY	0	0	0	3(1.4%)	0	0
INFECTIONS AND INFESTATIONS	8(3.6%)	0	0	2(<1.0%)	1(<1.0%)	0
PULPITIS DENTAL	1(<1.0%)	0	0	0	0	0
RHINITIS	1(<1.0%)	0	0	0	0	0
VIRAL UPPER RESPIRATORY TRACT INFECTION	6(2.7%)	0	0	2(<1.0%)	1(<1.0%)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1(<1.0%)	1(<1.0%)	0	3(1.4%)	0	0
LIGAMENT SPRAIN	0	0	0	1(<1.0%)	0	0
LIMB INJURY	0	0	0	1(<1.0%)	0	0
LIP INJURY	0	0	0	1(<1.0%)	0	0
POST-TRAUMATIC NECK SYNDROME	0	1(<1.0%)	0	0	0	0
WOUND	1(<1.0%)	0	0	0	0	0

* Version is 20.0.

NML 4mg = Nicorette Mint Lozenge 4 mg
NPL 4mg = Nicorette Peppermint Lozenge 4 mg

Generated by program: tab_ae_trt_emerg.sas at 12:47:32, 11/13/2017

System Organ Class Preferred Term Name	NML 4mg (N=225)						NPL 4mg (N=221)					
	Mild		Moderate		Severe		Mild		Moderate		Severe	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3	(1.3%)	0		0		0		1	(<1.0%)	0	
ARTHRALGIA	1	(<1.0%)	0		0		0		0		0	
MUSCLE TIGHTNESS	1	(<1.0%)	0		0		0		0		0	
NECK PAIN	1	(<1.0%)	0		0		0		0		0	
TORTICOLLIS	0		0		0		0		1	(<1.0%)	0	
NERVOUS SYSTEM DISORDERS	19	(8.4%)	7	(3.1%)	0		18	(8.1%)	4	(1.8%)	0	
DIZZINESS	0		0		0		1	(<1.0%)	0		0	
HEADACHE	15	(6.7%)	6	(2.7%)	0		17	(7.7%)	4	(1.8%)	0	
MIGRAINE	0		1	(<1.0%)	0		0		0		0	
PRESYNCOPE	1	(<1.0%)	0		0		0		0		0	
SOMNOLENCE	2	(<1.0%)	0		0		0		0		0	
SYNCOPE	1	(<1.0%)	0		0		0		0		0	
PSYCHIATRIC DISORDERS	1	(<1.0%)	0		0		0		0		0	
SLEEP DISORDER	1	(<1.0%)	0		0		0		0		0	
RENAL AND URINARY DISORDERS	0		0		0		1	(<1.0%)	0		0	
DYSURIA	0		0		0		1	(<1.0%)	0		0	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1	(<1.0%)	1	(<1.0%)	0		2	(<1.0%)	0		0	
DYSMENORRHOEA	1	(<1.0%)	1	(<1.0%)	0		2	(<1.0%)	0		0	

* Version is 20.0.

NML 4mg = Nicorette Mint Lozenge 4 mg
NPL 4mg = Nicorette Peppermint Lozenge 4 mg

Generated by program: tab_ae_trt_emerg.sas at 12:47:32, 11/13/2017

System Organ Class Preferred Term Name	NML 4mg (N=225)						NPL 4mg (N=221)					
	Mild		Moderate		Severe		Mild		Moderate		Severe	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	30	(13.3%)	4	(1.8%)	0		41	(18.6%)	6	(2.7%)	0	
COUGH	0		0		0		3	(1.4%)	0		0	
DYSPHONIA	0		0		0		1	(<1.0%)	0		0	
HICCUPS	5	(2.2%)	0		0		12	(5.4%)	1	(<1.0%)	0	
INCREASED UPPER AIRWAY SECRETION	1	(<1.0%)	0		0		0		0		0	
NASAL CONGESTION	2	(<1.0%)	0		0		0		0		0	
OROPHARYNGEAL PAIN	0		1	(<1.0%)	0		1	(<1.0%)	0		0	
PNEUMOTHORAX SPONTANEOUS	0		1	(<1.0%)	0		0		0		0	
RHINORRHOEA	0		0		0		3	(1.4%)	0		0	
THROAT IRRITATION	18	(8.0%)	3	(1.3%)	0		21	(9.5%)	4	(1.8%)	0	
THROAT TIGHTNESS	4	(1.8%)	0		0		4	(1.8%)	1	(<1.0%)	0	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4	(1.8%)	0		0		3	(1.4%)	2	(<1.0%)	0	
COLD SWEAT	3	(1.3%)	0		0		3	(1.4%)	2	(<1.0%)	0	
HYPERHIDROSIS	1	(<1.0%)	0		0		0		0		0	
VASCULAR DISORDERS	0		1	(<1.0%)	0		0		0		0	
THROMBOPHLEBITIS	0		1	(<1.0%)	0		0		0		0	

* Version is 20.0.

NML 4mg = Nicorette Mint Lozenge 4 mg
NPL 4mg = Nicorette Peppermint Lozenge 4 mg

Generated by program: tab_ae_trt_emerg.sas at 12:47:32, 11/13/2017

Subjects with Treatment Related Adverse Events:

Table 14.3.1.4 Subjects with Treatment Related Adverse Events Relation to treatment Possible, Probable or Very likely By System Organ Class and Preferred Term* Subjects in Safety Analysis Set

Table 14.3.1.4 (Page 1 of 2)
Subjects with Treatment Related Adverse Events
Relation to treatment Possible, Probable or Very likely
By System Organ Class and Preferred Term*
Subjects in Safety Analysis Set

System Organ Class Preferred Term Name	NML 4mg (N=225) n (%)	NPL 4mg (N=221) n (%)
SUBJECTS WITH AT LEAST ONE AE	64(28.4%)	81(36.7%)
CARDIAC DISORDERS	1(<1.0%)	1(<1.0%)
PALPITATIONS	1(<1.0%)	0
TACHYCARDIA	0	1(<1.0%)
EAR AND LABYRINTH DISORDERS	8(3.6%)	9(4.1%)
VERTIGO	8(3.6%)	9(4.1%)
EYE DISORDERS	1(<1.0%)	0
DRY EYE	1(<1.0%)	0
GASTROINTESTINAL DISORDERS	33(14.7%)	49(22.2%)
ABDOMINAL PAIN UPPER	1(<1.0%)	3(1.4%)
DRY MOUTH	1(<1.0%)	0
DYSPEPSIA	8(3.6%)	11(5.0%)
DYSPHAGIA	0	1(<1.0%)
ERUCTATION	1(<1.0%)	0
FLATULENCE	1(<1.0%)	1(<1.0%)
NAUSEA	24(10.7%)	36(16.3%)
ORAL DISCOMFORT	0	1(<1.0%)
SALIVARY HYPERSECRETION	0	4(1.8%)
STOMATITIS	0	1(<1.0%)
VOMITING	1(<1.0%)	1(<1.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3(1.3%)	2(<1.0%)
CHEST DISCOMFORT	3(1.3%)	1(<1.0%)
CHEST PAIN	1(<1.0%)	0
FATIGUE	0	1(<1.0%)

* Version is 20.0.

NML 4mg = Nicorette Mint Lozenge 4 mg
NPL 4mg = Nicorette Peppermint Lozenge 4 mg

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System Organ Class Preferred Term Name	NML 4mg (N=225) n (%)	NPL 4mg (N=221) n (%)
NERVOUS SYSTEM DISORDERS	14(6.2%)	12(5.4%)
HEADACHE	11(4.9%)	12(5.4%)
MIGRAINE	1(<1.0%)	0
SOMNOLENCE	2(<1.0%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	30(13.3%)	44(19.9%)
COUGH	0	3(1.4%)
DYSPHONIA	0	1(<1.0%)
HICCUPS	5(2.2%)	13(5.9%)
INCREASED UPPER AIRWAY SECRETION	1(<1.0%)	0
RHINORRHOEA	0	1(<1.0%)
THROAT IRRITATION	20(8.9%)	25(11.3%)
THROAT TIGHTNESS	4(1.8%)	5(2.3%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3(1.3%)	5(2.3%)
COLD SWEAT	3(1.3%)	5(2.3%)

* Version is 20.0.

NML 4mg = Nicorette Mint Lozenge 4 mg
NPL 4mg = Nicorette Peppermint Lozenge 4 mg

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Subjects with Treatment Related Adverse Events By Worst Case Severity:

Table 14.3.1.5 Subjects with Treatment Related Adverse Events Relation to treatment Possible, Probable or Very likely By System Organ Class, Preferred Term, and Worst Case Severity*

Table 14.3.1.5 (Page 1 of 2)
Subjects with Treatment Related Adverse Events
Relation to treatment Possible, Probable or Very likely
By System Organ Class, Preferred Term, and Worst Case Severity*

System Organ Class Preferred Term Name	NML 4mg (N=225) Mild n (%)	NML 4mg (N=225) Moderate n (%)	NML 4mg (N=225) Severe n (%)	NPL 4mg (N=221) Mild n (%)	NPL 4mg (N=221) Moderate n (%)	NPL 4mg (N=221) Severe n (%)
SUBJECTS WITH AT LEAST ONE AE	54(24.0%)	9(4.0%)	1(<1.0%)	65(29.4%)	15(6.8%)	1(<1.0%)
CARDIAC DISORDERS	1(<1.0%)	0	0	1(<1.0%)	0	0
PALPITATIONS	1(<1.0%)	0	0	0	0	0
TACHYCARDIA	0	0	0	1(<1.0%)	0	0
EAR AND LABYRINTH DISORDERS	8(3.6%)	0	0	9(4.1%)	0	0
VERTIGO	8(3.6%)	0	0	9(4.1%)	0	0
EYE DISORDERS	1(<1.0%)	0	0	0	0	0
DRY EYE	1(<1.0%)	0	0	0	0	0
GASTROINTESTINAL DISORDERS	30(13.3%)	2(<1.0%)	1(<1.0%)	43(19.5%)	5(2.3%)	1(<1.0%)
ABDOMINAL PAIN UPPER	1(<1.0%)	0	0	3(1.4%)	0	0
DRY MOUTH	1(<1.0%)	0	0	0	0	0
DYSPEPSIA	8(3.6%)	0	0	9(4.1%)	2(<1.0%)	0
DYSPHAGIA	0	0	0	1(<1.0%)	0	0
ERUCTATION	1(<1.0%)	0	0	0	0	0
FLATULENCE	1(<1.0%)	0	0	1(<1.0%)	0	0
NAUSEA	21(9.3%)	2(<1.0%)	1(<1.0%)	31(14.0%)	4(1.8%)	1(<1.0%)
ORAL DISCOMFORT	0	0	0	1(<1.0%)	0	0
SALIVARY HYPERSECRETION	0	0	0	3(1.4%)	1(<1.0%)	0
STOMATITIS	0	0	0	1(<1.0%)	0	0
VOMITING	0	0	1(<1.0%)	1(<1.0%)	0	0

* Version is 20.0.

NML 4mg = Nicorette Mint Lozenge 4 mg
NPL 4mg = Nicorette Peppermint Lozenge 4 mg

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System Organ Class Preferred Term Name	NML 4mg (N=225) Mild n (%)	NML 4mg (N=225) Moderate n (%)	NML 4mg (N=225) Severe n (%)	NPL 4mg (N=221) Mild n (%)	NPL 4mg (N=221) Moderate n (%)	NPL 4mg (N=221) Severe n (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3(1.3%)	0	0	1(<1.0%)	1(<1.0%)	0
CHEST DISCOMFORT	3(1.3%)	0	0	0	1(<1.0%)	0
CHEST PAIN	1(<1.0%)	0	0	0	0	0
FATIGUE	0	0	0	1(<1.0%)	0	0
NERVOUS SYSTEM DISORDERS	9(4.0%)	5(2.2%)	0	10(4.5%)	2(<1.0%)	0
HEADACHE	7(3.1%)	4(1.8%)	0	10(4.5%)	2(<1.0%)	0
MIGRAINE	0	1(<1.0%)	0	0	0	0
SOMNOLENCE	2(<1.0%)	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	27(12.0%)	3(1.3%)	0	38(17.2%)	6(2.7%)	0
COUGH	0	0	0	3(1.4%)	0	0
DYSPHONIA	0	0	0	1(<1.0%)	0	0
HICCUPS	5(2.2%)	0	0	12(5.4%)	1(<1.0%)	0
INCREASED UPPER AIRWAY SECRETION	1(<1.0%)	0	0	0	0	0
RHINORRHOEA	0	0	0	1(<1.0%)	0	0
THROAT IRRITATION	17(7.6%)	3(1.3%)	0	21(9.5%)	4(1.8%)	0
THROAT TIGHTNESS	4(1.8%)	0	0	4(1.8%)	1(<1.0%)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3(1.3%)	0	0	3(1.4%)	2(<1.0%)	0
COLD SWEAT	3(1.3%)	0	0	3(1.4%)	2(<1.0%)	0

* Version is 20.0.

NML 4mg = Nicorette Mint Lozenge 4 mg
NPL 4mg = Nicorette Peppermint Lozenge 4 mg

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4.2.2 Study NICTDP1076

Title of Study:
Comparative pharmacokinetic study of new oral nicotine replacement therapy products – A study in healthy smokers.

Reviewer comments: *There are no issues identified with the Applicant's synopsis report.*

The following synopsis report was provided by the Applicant:

SYNOPSIS
Investigators: (b)(4)
Study Centers:
(b)(4)

Publication (reference): None
Study Period: Date of first enrollment: 31 August 2009
Date of last completed: 03 December 2009
Phase of Development: Phase 1
Objective:
The primary objective of this study was to demonstrate bioequivalence between NSL2L and NiQuitin™ ('NiQuitin') lozenge 2 mg, and between NSL4M and NiQuitinTM lozenge 4 mg. The maximum baseline-corrected observed nicotine concentrations (cCmax), and the baseline corrected areas under the concentration-vs.-time curves until the last measurable concentration and until infinity (cAUCt and cAUC∞), obtained after single-dose administration of the investigational products, were used as parameters for comparison.
Secondary objectives were:
- to describe the single-dose pharmacokinetics of NSL4L and NSL4H. The parameters described were cCmax, cAUCt and cAUC∞,
- to evaluate the time at which the maximum concentration was observed (tmax), the terminal elimination rate constant (λz) and the terminal half-life (t1/2) for the NSL (b)(4) and NiQuitinTM lozenge,
- to evaluate the tolerability and safety,
- to describe the time course of urges to smoke,
- to evaluate the palatability,
- to evaluate irritation in mouth and throat,
- to evaluate the time until complete tablet dissolution in the mouth.

Methodology:
The study was a single-dose, randomized, crossover study with 104 subjects. The practical performance of the study including health screening and performance of treatments were conducted at two sites, with 52 subjects at each site. The investigational products (i.e. one (b)(4) NSL 2 mg, (b)(4) of NSL 4 mg, NiQuitin lozenge 2 and 4 mg) were given as single doses at separate visits. Periods without NRT, lasting for at least 36 hours, separated treatment visits.

Subjects received five of the six investigational products, i.e. the two [redacted] (b)(4) (NSL2L and NSL4M) and the two references (NiQuitin lozenge 2 and 4 mg), and one of the [redacted] (b)(4) (NSL4L or NSL4H).
At treatment visits, blood samples for pharmacokinetic analyses (of nicotine in plasma) were drawn before and at 7.5, 15, 20, 30, 40, 50, and 60 minutes, as well as at 1.25, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after start of drug administration.
Urges to smoke were rated (using a Likert scale with four ordered categories) before and at 2, 5, 10, 15, 20, 25, 30, 45, and 60 minutes after start of administration. Palatability was measured with a 100 mm visual analogue scale (VAS) immediately after dissolution of the product. Irritation in mouth/throat was measured with a 100 mm VAS before and at 5 minutes after start of administration, as well as immediately after dissolution of the product. The time until complete tablet dissolution was recorded. Subjects were monitored to capture any adverse events that occurred. The study was open in the sense that subjects and study personnel were aware of which treatment was administered at a given visit. However, bioanalysts and pharmacokineticist were not aware of treatment labels except when analyzing data from period 5 (after completion and database lock for all remaining analyses). When all analyses of treatments AD were finalized, the randomization list was released for statistical evaluation and therefore it was open for pharmacokineticists when treatments E and F were assessed.

Number of Subjects (planned and analyzed):
One-hundred and four (104) subjects were planned and included. One-hundred (100) completed the study.

Diagnosis and Main Criteria for Inclusion:
Healthy male and female subjects between the ages of 19 and 50 years, inclusive, smoking at least 10 cigarettes daily during at least one year preceding inclusion were enrolled. The subjects had to have a Body Mass Index (BMI) between 17.5 and 30.0 kg/m2 and a total body weight ≥50 kg. Females had to be in a postmenopausal/perimenopausal state with absence of menstrual discharge for at least two years and a serum FSH level exceeding 30 IU/L, or in a premenopausal/perimenopausal state with effective contraception (oral, injected or implanted hormonal contraceptives, intrauterine devices or status after operative sterilization).

Test Product, Dose and Mode of Administration, Batch Number:
Table S1 provides information of the investigational products.

Table S1 Investigational Products and Identity

Investigational Product	Form	Nicotine Dose	Vendor Lot ID / Batch Number
NSL2L	Lozenge	2 mg	LFT1694
NiQuitin™	Lozenge	2 mg	2018060
NSL4M	Lozenge	4 mg	LFT1696
NiQuitin™	Lozenge	4 mg	2018483
NSL4L	Lozenge	4 mg	LFT1699
NSL4H	Lozenge	4 mg	LFT1700

In contrast to customary terminology, oral route of administration in this study does not entail the swallowing of the lozenge but a complete dissolution in the oral cavity

Duration of Treatment:
One-hundred (100) subjects received five single doses of the investigational products (NSL2L, NiQuitin lozenge 2 mg, NSL4M, NiQuitin lozenge 4 mg and either of NSL4L or NSL4H) on separate treatment visits. Four subjects did not receive all doses (two subjects due to pregnancy, one subject was withdrawn due to poor compliance, and one subject discontinued because he/she was no longer willing to participate). Periods of at least 36 hours separated the treatment visits.

Criteria for Evaluation:
All subjects who received treatments and who were not involved in any major protocol deviations were included in the statistical analysis. The statistical analyses were assessed separately for the two doses (2 mg and 4 mg). Any missing data were assumed to be missing at random. No imputation of missing data was performed. Carryover effects were assumed ignorable. All subjects who received at least one dose of treatment were included in the safety analysis set.

Statistical Methods:
An analysis of variance (ANOVA) model encompassing subject (considered random and nested in sequence), period, sequence, treatment and site was fitted to the data after logarithmic transformation of baseline corrected Cmax, AUCt, and AUC∞. For the response parameters, bioequivalence was concluded if the 90% confidence interval for the corresponding comparison □Test/□Standard was entirely within the equivalence interval (80%, 125%).
Some descriptive statistics were calculated and tabulated, including mean, standard deviation, median, maximum and minimum values for the pharmacokinetic parameters, palatability, irritation in mouth and throat, and the time until complete tablet dissolution. For tmax the frequency distribution was tabulated for each treatment. For urges to smoke, the frequency distribution was tabulated for each treatment and time point.

SUMMARY – CONCLUSIONS
Pharmacokinetic and Pharmacodynamic Results:
Pharmacokinetic parameters:
Figure S1 and Figure S2 present the average plasma concentration profiles for the treatments over 12 hours after start of administration. In Table S2 and Table S3 the pharmacokinetic parameters for the investigational products are shown. Table S4 and Table S5 show mean ratios and corresponding 90% confidence intervals for ratios of pharmacokinetic parameters between NSL2L and NiQuitin lozenge 2 mg, and NSL4L/NSL4M/NSL4H and NiQuitin lozenge 4 mg, respectively.

Figure S1 Mean Plasma Concentration versus Time Profiles over 12 hours after Administration of the 2 mg Products

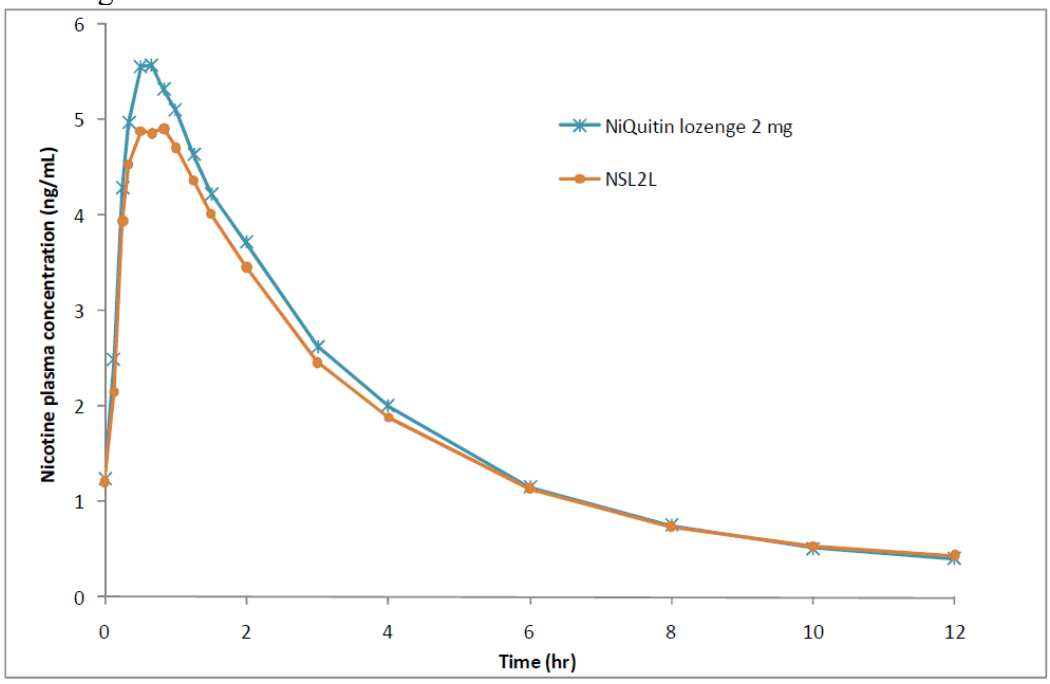

Figure S2 Mean Plasma Concentration versus Time Profiles over 12 hours after Administration of the 4 mg products

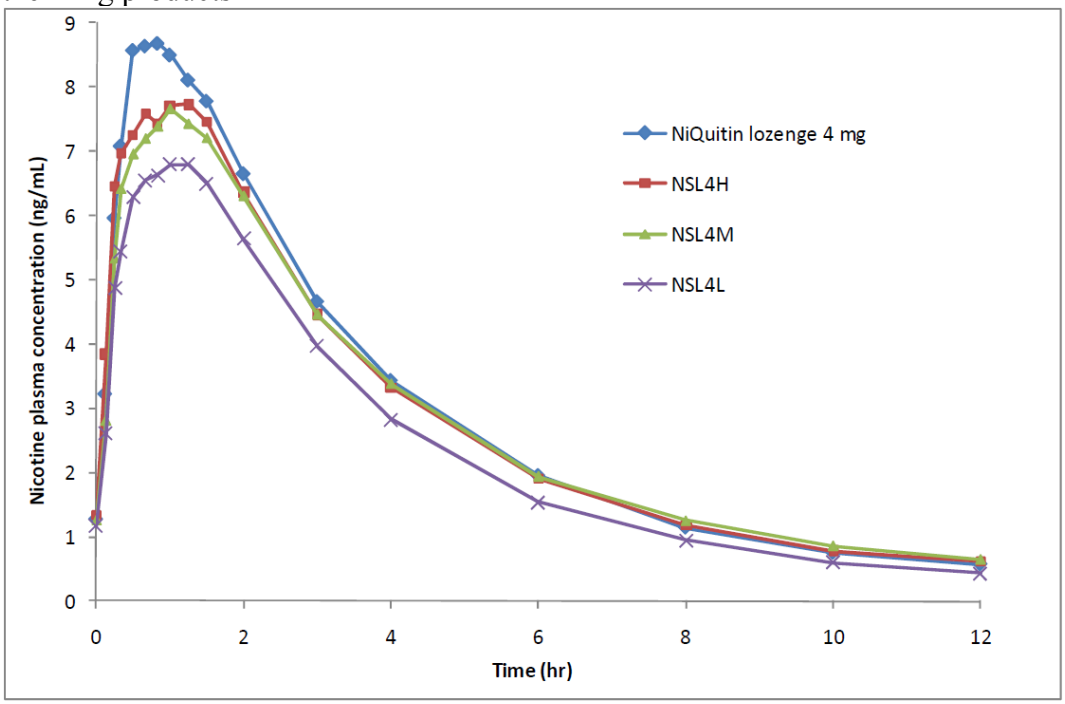

Table S2 Pharmacokinetic Parameters for the 2 mg Products (Mean (SD))

Treatment	**n**	**cC_{max} (ng/mL)**	**t_{max}* (min)**	**$cAUC_t$ (ng/mLxh)**	**$cAUC_\infty$ (ng/mLxh)**	**$t_{1/2}$ (h)**
NSL2L	94	4.9 (1.7	40	13 7 7.0)	16.0 (8.6)	3.1
NiQuitin™ lozenge 2 mg	96	5.4 (1.9)	30	14 9 6.4)	16.9 (7.0)	2.9

Source: Table 14.2.2
* Median

Table S3 Pharmacokinetic Parameters for the 4 mg Products (Mean (SD))

Treatment	**n**	**cC_{max} (ng/mL)**	**t_{max}* (min)**	**$cAUC_t$ (ng/mLxh)**	**$cAUC_\infty$ (ng/mLxh)**	**$t_{1/2}$ (h)**
NSL4L	46	7.3 (2.7)	50	23 5 9.7)	25.7 (10.0)	2.8
NSL4M	97	8.1 (3.4)	50	27.6 (16.8)	30.8 (20.5)	3.1
NSL4H	50	8.6 (3.4)	40	27.6 (14.0)	30.6 (16.9)	3.0
NiQuitin™ lozenge 4 mg	99	9.3 (2.8)	40	29.3 (11.6)	32.0 (13.6)	3.0

Source: Table 14.2.2
* Median

Table S4 Estimated Pharmacokinetic Parameter Ratios with 90% CI for the 2 mg Products

	NSL2L/ NiQuitin™ lozenge 2 mg (n=94-96)	
	Ratio	Interval
cC_{max}	89.3%	84.2-94.8%
$cAUC_t$	90.5%	86.1-95.2%
$cAUC_{\square}$	92.1%	87.7-96.6%

Source: Table 14.2.2

Table S5 Estimated Pharmacokinetic Parameter Ratios with 90% CI for the 4 mg Products

	NSL4L/ NiQuitin™ lozenge 4 mg (n=46)		**NSL4M/ NiQuitin™ lozenge 4 mg (n=97-99)**		**NSL4H/ NiQuitin™ lozenge 4 mg (n=50)**	
	Ratio	**Interval**	**Ratio**	**Interval**	**Ratio**	**Interval**
cC_{max}	78.5%	71.5-86.2%	85.5%	81.0-90.4%	90.8%	82.9-99.4%
$cAUC_t$	80.5%	72.8-89.0%	88.1%	83.9-92.4%	90.6%	82.1-99.9%
$cAUC_\infty$	80.6%	72.3-90.0%	88.7%	84.7-92.9%	93.3%	83.9-103.8%

Source: Table 14.2.2

Palatability:
Results of the palatability measurements are given in Table S6 and Table S7. On the VAS used, 0 mm corresponded to “very unpleasant” and 100 mm corresponded to “most pleasant”.

Table S6 Palatability of the 2 mg Products (Mean (SD))

Treatment	n	mm
NSL2L	94	61 (25)
NiQuitin™ lozenge 2 mg	96	60 (21)

Source: Table 14.2.4

Table S7 Palatability of the 4 mg Products (Mean (SD))

Treatment	n	mm
NSL4L	46	47 (23)
NSL4M	97	57 (24)
NSL4H	50	43 (25)
NiQuitin™ lozenge 4 mg	99	56 (23)

Source: Table 14.2.4

Irritation in mouth and throat:
The across-subject means and standard deviations for mouth and throat irritation are presented in Table S8 and Table S9. On the VAS used, 0 mm corresponded to "not at all" and 100 mm corresponded to "worst imaginable."

Table S8 Irritation in Mouth and Throat for the 2 mg Products (mm, Mean (SD))

Treatment	n	Prior to treatment	5 min	After dissolution
NSL2L	94	4 (11)	25 (22)	24 (22)
NiQuitin™ lozenge 2 mg	95	2 (8)	20 (17)	15 (18)

Source: Table 14.2.5

Table S9 Irritation in Mouth and Throat for the 4 mg Products (mm, Mean (SD))

Treatment	n	Prior to treatment	5 min	After dissolution
NSL4L	46	3 (9)	43 (23)	35 (27)
NSL4M	97	3 (9)	31 (25)	27 (24)
NSL4H	50	1 (4)	44 (30)	34 (27)
NiQuitin™ lozenge 4 mg	99	2 (8)	26 (23)	21 (21)

Source: Table 14.2.5

Dissolution Time:
Table S10 and Table S11 provide across-subject averages and standard deviations for times until complete dissolution of the tablets in the mouth.

Table S10 Dissolution Times of the 2 mg Products (minutes)

Treatment	n	Mean (SD)	Min – Max
NSL2L	94	16.8 (5.5)	7 – 37
NiQuitin™ lozenge 2 mg	96	24.6 (11.2)	11 – 68

Source: Table 14.2.6

Table S11 Dissolution Times of the 4 mg Products (minutes)

Treatment	n	Mean	Min – Max
NSL4L	46	16.1 (6.6)	8 – 42
NSL4M	97	17.5 (7.5)	7 – 51
NSL4H	50	15.9 (7.2)	8 – 52
NiQuitin™ lozenge 4 mg	99	26.3 (12.0)	11 – 84

Source: Table 14.2.6

Safety Results:
There were no SAEs in this study. A total of 182 treatment-emergent AEs were reported. Ninety-seven (97) of these AEs were judged to be possibly treatment-related. One (1) of the AEs was categorized as severe, 38 were moderate and 58 were of mild intensity. Table S12 provides information about the numbers of subjects experiencing treatment-related AEs. Of the treatment-related AEs reported in this study, 14 were reported (by 12 subjects) for NSL2L, 10 (by 7 subjects) for NiQuitin lozenge 2 mg, 16 (by 12 subjects) for NSL4L, 31 (by 23 subjects) for NSL4M, 12 (by 9 subjects) for NSL4H and 14 (by 12 subjects) for NiQuitin lozenge 4 mg. The body system most affected by AEs was the gastrointestinal tract, with nausea as the most frequently reported. There were no indications that the types of AEs of the NSL (b)(4) differ from those of other oral nicotine replacement products.

Table S12 Overview of Treatment-related Adverse Events

Body System Preferred term	**NSL2L** (n=101)	**NiQuitin™ 2 mg** (n=101)	**NSL4L** (n=49)	**NSL4M** (n=103)	**NSL4H** (n=51)	**NiQuitin™ 4 mg** (n=104)
Gastrointestinal disorders						
Abdominal distension	1	1		1		
Abdominal pain upper				1		1
Cheilitis	1					
Dyspepsia	2	2	3	3	2	
Eructation			1			
Flatulence				1	1	
Nausea	3	3	4	9*	4	4
Saliva altered					1	
Saliva hypersecretion		1		2		1
General disorders and administration site conditions						
Chest discomfort			1			
Fatigue	1					
Infections and infestations						
Nasopharyngitis		1		1		
Nervous system disorders						
Dizziness			1	2		
Headache		1		3		1
Respiratory, thoracic and mediastinal disorders						
Cough	2		4	4		
Dyspnoea			1			1
Hiccups	2				2	2
Nasal congestion					1	1
Oropharyngeal pain	1					1
Sneezing						1
Throat irritation	1			1		
Throat tightness		1	1	3	1	1

* 1 event rated as severe

Source: Table 14.3.1.2 and Table 14.3.1.3

Conclusions:
 Bioequivalence was demonstrated between NSL2L and NiQuitin lozenge 2 mg, as well as between NSL4M and NiQuitinTM lozenge 4 mg.
 Palatability was similar for the pivotal NSL prototypes and the NiQuitin lozenges in this study.
 Coating of the NSL prototypes seems to decrease irritation in mouth and throat.
 The NSL prototypes seem to dissolve faster in the mouth than the NiQuitin lozenges in this study.
 There were no indications that the types of AE of the NSL prototypes differ from those of other oral nicotine replacement products.

Date of the Report: 31 May 2010

Additional information pertinent from the main study report:

Rationale:
As part of the product development program for NSL, the current study was performed to test whether NSL 2 mg nicotine, with a low level of buffer capacity, (NSL2L) and NSL 4 mg nicotine, with a medium level of buffer capacity, (NSL4M) were bioequivalent with NiQuitinTM lozenge 2 and 4 mg, respectively. NSL2L and NSL4M were of (b)(4) and coated. Two uncoated prototypes (b)(4), NSL4L (NSL 4 mg nicotine, with a low level of buffer capacity) and NSL4H (NSL 4 mg nicotine, with a high level of buffer capacity), were included in the study to gain more understanding on buffer level effect on pharmacokinetic and pharmacodynamic parameters.

Inclusion Criteria:
Subjects were required to fulfill all of the following criteria for inclusion in the study:
1. Healthy male or female subjects between the ages of 19 and 50 years, inclusive. Health is defined as the absence of clinically relevant abnormalities identified by a detailed medical history, physical examination, blood pressure and pulse rate measurements, 12-lead electrocardiogram as well as clinical laboratory tests, as judged by the investigator or co-investigator.
2. Smoking of at least 10 cigarettes daily during at least one year preceding inclusion.
3. For females: Postmenopausal state (absence of menstrual discharge for at least two years and a serum FSH level exceeding 30 IU/L) or premenopausal/perimenopausal state with effective contraception (oral, injected or implanted hormonal contraceptives, intrauterine device or status after operative sterilization).
4. Body Mass Index (BMI) between 17.5 and 30.0 kg/m2 and a total body weight >-50.0 kg.
5. A personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
6. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures specified in the protocol.

Exclusion Criteria:
Subjects presenting with any of the following were not included in the study:
7. Evidence or history of an acute or chronic medical or psychiatric condition or allergy or laboratory abnormality, or of use of drugs that, in the judgment of the investigator or co-

investigator, may increase the risk associated with study participation or interfere with the interpretability of study results.
8. Females: Pregnancy, breast-feeding, premenopausal, or perimenopausal, state with insufficient contraception as specified under Inclusion Criteria.
9. History of regular alcohol consumption in the 6 months before screening exceeding weekly limits of 2 L of wine or 5 L of beer or 0.6 L of spirits for females and 3 L of wine or 7.5 L of beer or 0.9 L of spirits for males. The investigator may lower these limits if a subject consumes different types of alcoholic beverages.
10. Treatment with an investigational drug within 3 months preceding the first dose of study treatment.
11. Donation or loss of blood within 3 months prior to the first treatment visit if the estimated lost blood volume equaled or exceeded 450 mL.
12. Known sensitivity to heparin or history of heparin-induced thrombocytopenia.
13. Pathological oral status interfering with normal muscular, sensory, or absorptive function of the oral cavity.

Selection and Timing of Dose for Each Subject:
In this study, each treatment included a single-dose administration of the investigational products (i.e. one prototype of NSL 2 mg, three prototypes of NSL 4 mg, NiQuitin lozenge 2 and 4 mg) given in the morning on separate days. Periods of at least 36 hours separated the treatment visits. Subjects abstained from using nicotine-containing products (besides treatments specified in the protocol) and smoking from 12 hours before and throughout each treatment visit. *Subjects were requested to have breakfast at home before coming to the trial site. Meals during treatment visits were provided at the trial site. Subjects did not eat or drink from 15 minutes before until 60 minutes after the start of drug administration.* Subjects abstained from strenuous exercise from 10 hours before and until the end of screening and treatment visits. Subjects abstained from alcohol from 24 hours before and throughout each treatment visit.

Prior and Concomitant Therapy:
Concomitant therapy considered necessary for the subject's welfare could be given at the discretion of the investigator. If necessary, medications for acute complaints and diseases could be given without prior consultation with the investigator, although this could result in the withdrawal of the subject from the study. In all other cases, subjects had to abstain from using concomitant medication from 14 days prior to the first treatment visit and throughout the study. Medication taken at some time between 14 days before the screening visit and the end of the last treatment visit was listed as Previous and Concomitant Medication in the CRF. Records included start and stop dates of administration and if possible daily dose. If the stop date occurred after the end of the last treatment visit, the medication was classified as ongoing. Subjects were asked about concomitant medication at each study visit.

Blood Samples:
Samples of 3 mL blood were collected in heparinized gel tubes. All efforts were made to obtain blood samples at exact nominal times. The real time points for sampling were recorded. Blood samples were cooled down (b)(4) Plasma was transferred into screw-capped polypropylene tubes, (b)(4).

Pharmacokinetic Analytical Methods:
Samples of nicotine in plasma from treatments A, B, C and D were analyzed before samples from treatments E and F. Nicotine in plasma was analyzed in accordance with method (b)(4) at the (b)(4) *The lower limit of quantification (LLOQ) with the current method was 0.5 ng/mL*. Normally, the samples were analyzed once. However, for pharmacokinetic reasons, the pharmacokineticist appointed for the study was allowed to make a written request for reanalysis of selected samples. Such samples were reanalyzed in triplicates, if possible, with the plasma remaining after the initial analysis. If the remaining plasma volume was too small for a reanalysis, the corresponding concentration value was to be regarded as a missing data point. The pharmacokineticist was not aware of the plasma volume remaining after the first bioanalysis and, thus, outlier identification was made independently of the availability of a second bioanalysis. The reason for reanalysis was documented in the study file.

Calculation of Pharmacokinetic Parameters:
Individual plasma concentration data from each subject and the corresponding blood sampling times were the basic data for pharmacokinetic analyses. Ordinarily, nominal sampling times were used; however, actual sampling times were used whenever they deviated by more than 1 minute from the nominal times. For subject-level analyses, plasma concentrations below the LLOQ and observed before tmax were set to LLOQ/2, whereas concentrations below the LLOQ and observed after tmax were omitted. When calculating descriptive statistics for plasma concentrations across subjects for separate sampling times, all values below LLOQ were set to LLOQ/2. Data from treatment visits with baseline nicotine concentrations exceeding 5 ng/mL were excluded from the pharmacokinetic evaluation. The calculations were performed using WinNonlin Professional (version 5.2, Pharsight Corporation, Mountain View, CA, USA). Output was checked against the bioanalytical data. Cmax, AUCt and AUC_∞ were corrected for nicotine baseline concentrations according to the following equations, where C0 is the baseline nicotine concentration:

$cC_{max} = C_{max} - C_0 \cdot e^{-\lambda z \, tmax}$

$cAUC_t = cAUC_\infty - ((C_t - C_0 \cdot e^{-\lambda z \cdot t}) / \lambda_Z)$, where t is the last time point with a concentration exceeding LLOQ

$cAUC_\infty = AUC_\infty - C_0/\lambda_Z$

Statistical and Analytical Plans:
All subjects who received treatment and who were not involved in any major protocol deviations were included in the statistical analysis. The statistical analyses were assessed separately for the two doses (2 mg and 4 mg). Any missing data were assumed to be missing at random. No imputation of missing data was performed. Carryover effects were assumed ignorable. An analysis of variance (ANOVA) model encompassing subject (considered random and nested in sequence), period, sequence, treatment and site was fitted to the data after logarithmic transformation of *baseline corrected Cmax, AUCt, and AUC∞*. For the response parameters, bioequivalence was concluded if the 90% confidence interval for the corresponding comparison $\mu_{Test}/\mu_{Standard}$ was

entirely within the equivalence interval (80%, 125%). Some descriptive statistics were calculated and tabulated, including mean, standard deviation, median, maximum and minimum values for the pharmacokinetic parameters, palatability, irritation in mouth and throat, and the time until complete tablet dissolution. For tmax the frequency distribution was tabulated for each treatment. For urges to smoke, the frequency distribution was tabulated for each treatment and time point. The statistical methods outlined here are those that were specified in the Statistical Analysis Plan (SAP) prepared for this study. The SAP provided extensive elaboration and clarification of the statistical methods given in the Protocol and, therefore, superseded the protocol specified methods. All changes specified in the Statistical Analysis Plan were made prior to breaking the study blind and none were made as a result of any deviations in the planned conduct of the study.

Determination of Sample Size:
The sample size calculation was based on previous data from two studies, A6431114 [5] and NICTDP1071 [6]. In A6431114 (b)(4) NNL (New Nicotine Lozenge) 2 mg were compared with NICORETTE® Gum 2 mg and in NICTDP1071 NML (Nicotine Mint Lozenge) 2 mg (same as NNL 2 mg, (b)(4) and NML 4 mg were compared with NICORETTE® Gum 2 mg and 4 mg. From the A6431114 study the root mean square error (MSE) from the ANOVA was found to be 0.27 and in NICTDP1071 the root MSE was 0.32. Given that 0.33 was the true root MSE and that the true ratio from the comparison of NSL2L and NiQuitin lozenge 2 mg for Cmax is 1.08, 90 subjects were needed to conclude bioequivalence at a significance level of 5% and a power of 90% for a total power of 80%. Since there were eight treatment sequences in the study and to compensate for possible withdrawals, 104 subjects were randomized.

Data Sets Analyzed:
There were 15 subjects with invalid pharmacokinetic parameters due to nicotine baseline concentrations ≥5.0 ng/mL at one or more of the treatment sessions. Data from the treatment sessions with valid pharmacokinetic parameter results from these subjects were included in the PK and PD analyses. Data from all 104 randomized subjects were analyzed with respect to safety information.

Demography and Baseline Characteristics:
In this study, 104 subjects (52 males and 52 females) were included (Table 14.1.2). One hundred-one (101) subjects were white and 3 were classed as "other". The subjects were smokers consuming on average 17.0 cigarettes per day (range 10-30 cigarettes) and had been smokers for 15.1 years on average (range 2-38 years). Their average age was 31.7 years (range 19-50 years), and their average BMI was 24.0 kg/m2 (range 18.3-29.8 kg/m2). Thus, smoking habits, age and BMI were in accordance with the inclusion criteria. All subjects were healthy adult volunteers. None of the subjects had conditions or a medical history that the investigator considered sufficient to affect the interpretability of study results or to represent a potential risk to the subject during study participation.

Safety:
All investigational products were well tolerated and no safety issues were identified. The most common adverse events reported derived from the gastrointestinal tract (mainly nausea). The types of adverse events of the NSL (b)(4) this study population,

appeared to be similar to that of NiQuitin™ lozenge and, thus, of other oral nicotine replacement products.

Appendix:
Demography and Baseline Characteristics:

Table 14.1.2 Demography and Baseline Characteristics All randomized subjects

Table 14.1.2 (Page 1 of 2)
Demography and Baseline Characteristics
All randomized subjects

Variable	All randomized subjects (N=104)
Age (years)	
N	104
Mean	31.7
S.D.	8.9
Median	29.0
Min-Max	(19-50)
Race	
White	101(97.1%)
Other	3(2.9%)
Total	104(100%)
Sex	
Male	52(50.0%)
Female	52(50.0%)
Total	104(100%)
BMI (kg/m 2)	
N	104
Mean	24.0
S.D.	2.8
Median	23.9
Min-Max	(18.3-29.8)
Years smoking	
N	104
Mean	15.1
S.D.	8.4
Median	14.0
Min-Max	(2-38)
Cigarettes/day	
N	104
Mean	17.0
S.D.	4.1
Median	17
Min-Max	(10-30)
FTND	
N	104
Mean	4.6
S.D.	1.8
Median	5
Min-Max	(0-9)

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Table 14.2.2.1 Pharmacokinetic Parameters Summary Statistics and Treatment Comparisons: NSL2L vs. NiQuitinTM lozenge 2 mg Subjects in Full Analysis Set

Parameter	NSL2L	NiQuitinTM lozenge 2 mg
Tmax (hr)		
0.13	1(1.1%)	0
0.25	10(10.6%)	7(7.3%)
0.33	14(14.9%)	24(25.0%)
0.35	1(1.1%)	0
0.50	18(19.1%)	20(20.8%)
0.67	13(13.8%)	17(17.7%)
0.75	0	1(1.0%)
0.83	18(19.1%)	7(7.3%)
1.00	8(8.5%)	14(14.6%)
1.25	5(5.3%)	2(2.1%)
1.50	4(4.3%)	2(2.1%)
2.00	2(2.1%)	2(2.1%)
Total	94(100%)	96(100%)
Lambda z (1/hr)		
N	94	96
Mean	0.26	0.27
S.D.	0.10	0.10
Median	0.23	0.26
Min-Max	(0.09-0.51)	(0.12-0.77)
Terminal half life (hr)		
N	94	96
Mean	3.12	2.87
S.D.	1.19	0.99
Median	3.04	2.66
Min-Max	(1.36-7.49)	(0.90-5.95)

* Corrected for baseline level

NSL2L = NSL 2 mg, Low level of buffer capacity
NiQuitinTM lozenge 2 mg = NiQuitinTM lozenge 2 mg

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Table 14.2.2.2 Pharmacokinetic Parameters Summary Statistics and Treatment Comparisons: NSL4M vs. NiQuitinTM lozenge 4 mg Subjects in Full Analysis Set

Parameter	NSL4M	NiQuitinTM lozenge 4 mg
Tmax (hr)		
0.25	8(8.2%)	3(3.0%)
0.33	13(13.4%)	15(15.2%)
0.50	15(15.5%)	21(21.2%)
0.67	6(6.2%)	17(17.2%)
0.83	10(10.3%)	7(7.1%)
1.00	18(18.6%)	12(12.1%)
1.02	1(1.0%)	0
1.25	11(11.3%)	12(12.1%)
1.50	12(12.4%)	9(9.1%)
2.00	2(2.1%)	3(3.0%)
3.00	1(1.0%)	0
Total	97(100%)	99(100%)
Lambda z (1/hr)		
N	97	99
Mean	0.25	0.27
S.D.	0.09	0.09
Median	0.23	0.25
Min-Max	(0.10-0.59)	(0.11-0.63)
Terminal half life (hr)		
N	97	99
Mean	3.10	2.96
S.D.	1.11	1.09
Median	3.00	2.76
Min-Max	(1.17-6.85)	(1.10-6.51)

* Corrected for baseline level

NSL4M = NSL 4 mg, Medium level of buffer capacity
NiQuitinTM lozenge 4 mg = NiQuitinTM lozenge 4 mg

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Table 14.2.2.3 Pharmacokinetic Parameters Summary Statistics and Treatment Comparisons: NSL4L and NSL4H vs. NiQuitinTM lozenge 4 mg Subjects in Full Analysis Set

Parameter	NiQuitinTM lozenge 4 mg	NSL4L	NSL4H
Tmax (hr)			
0.13	0	0	1(2.0%)
0.25	3(3.0%)	5(10.9%)	8(16.0%)
0.33	15(15.2%)	4(8.7%)	10(20.0%)
0.50	21(21.2%)	4(8.7%)	4(8.0%)
0.67	17(17.2%)	6(13.0%)	6(12.0%)
0.83	7(7.1%)	5(10.9%)	2(4.0%)
1.00	12(12.1%)	6(13.0%)	7(14.0%)
1.25	12(12.1%)	6(13.0%)	7(14.0%)
1.50	9(9.1%)	5(10.9%)	3(6.0%)
2.00	3(3.0%)	4(8.7%)	2(4.0%)
3.00	0	1(2.2%)	0
Total	99(100%)	46(100%)	50(100%)
Lambda z (1/hr)			
N	99	46	50
Mean	0.27	0.27	0.26
S.D.	0.09	0.08	0.08
Median	0.25	0.26	0.25
Min-Max	(0.11-0.63)	(0.12-0.53)	(0.12-0.47)
Terminal half life (hr)			
N	99	46	50
Mean	2.96	2.80	2.97
S.D.	1.09	0.83	0.94
Median	2.76	2.69	2.76
Min-Max	(1.10-6.51)	(1.31-5.74)	(1.47-5.63)

* Corrected for baseline level

NiQuitinTM lozenge 4 mg = NiQuitinTM lozenge 4 mg
NSL4L = NSL 4 mg, Low level of buffer capacity
NSL4H = NSL 4 mg, High level of buffer capacity

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Tablet Dissolution Time: NSL2L and NiQuitinTM lozenge 2 mg:

Table 14.2.6.1 (Page 1 of 1) Tablet Dissolution Time Subjects With Valid Pk data NSL2L and NiQuitinTM lozenge 2 mg

Dissolution time (minutes)	NSL2L	NiQuitinTM 2 mg
N	94	96
Mean	16.8	24.6
Std	5.54	11.21
Median	15.0	21.5
Min, Max	(7,37)	(11,68)

NSL2L = NSL 2 mg, Low level of buffer capacity
NiQuitinTM 2 mg = NiQuitinTM lozenge 2 mg

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Tablet Dissolution Time: NSL4M and NiQuitinTM lozenge 4 mg:

Table 14.2.6.2 (Page 1 of 1) Tablet Dissolution Time Subjects With Valid Pk data NSL4M and NiQuitinTM lozenge 4 mg

Dissolution time (minutes)	NSL4M	NiQuitinTM 4 mg
N	97	99
Mean	17.5	26.3
Std	7.49	11.97
Median	16.0	23.0
Min, Max	(7,51)	(11,84)

NSL4M = NSL 4 mg, Medium level of buffer capacity
NiQuitinTM 4 mg = NiQuitinTM lozenge 4 mg

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Tablet Dissolution Time: NSL4L and NSL4H:

Table 14.2.6.3 (Page 1 of 1) Tablet Dissolution Time Subjects With Valid Pk data NSL4L and NSL4H

Dissolution time (minutes)	NSL4L	NSL4H
N	46	50
Mean	16.1	15.9
Std	6.55	7.19
Median	15.5	14.0
Min, Max	(8,42)	(8,52)

NSL4L = NSL 4 mg, Low level of buffer capacity
NSL4H = NSL 4 mg, High level of buffer capacity

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Subjects with Adverse Events By System Organ Class and Preferred Term:

Table 14.3.1.1 Subjects with Adverse Events By System Organ Class and Preferred Term Subjects in Safety Analysis Set

Body System Preferred Term	NSL2L (N=101) n (%)	NiQuitinTM 2 mg (N=101) n (%)	NSL4M (N=103) n (%)	NiQuitinTM 4 mg (N=104) n (%)	NSL4L (N=49) n (%)
SUBJECTS WITH AT LEAST ONE AE	23(22.8)	18(17.8)	37(35.9)	31(29.8)	14(28.6)
Eye disorders	1(<1.0)	0	0	0	0
Blepharitis	1(<1.0)	0	0	0	0
Gastrointestinal disorders	7(6.9)	6(5.9)	17(16.5)	7(6.7)	7(14.3)
Abdominal distension	1(<1.0)	1(<1.0)	1(<1.0)	0	0
Abdominal pain	0	0	1(<1.0)	0	0
Abdominal pain upper	0	0	2(1.9)	1(<1.0)	0
Cheilitis	1(<1.0)	0	0	0	0
Diarrhoea	0	0	1(<1.0)	0	0
Dyspepsia	3(3.0)	2(2.0)	3(2.9)	1(<1.0)	3(6.1)
Eructation	0	0	0	0	1(2.0)
Flatulence	0	0	1(<1.0)	0	0
Nausea	3(3.0)	3(3.0)	10(9.7)	5(4.8)	4(8.2)
Saliva altered	0	0	0	0	0
Salivary hypersecretion	0	1(<1.0)	2(1.9)	1(<1.0)	0

NSL2L = NSL 2 mg, Low level of buffer capacity
NiQuitinTM 2 mg = NiQuitinTM lozenge 2 mg
NSL4M = NSL 4 mg, Medium level of buffer capacity
NiQuitinTM 4 mg = NiQuitinTM lozenge 4 mg
NSL4L = NSL 4 mg, Low level of buffer capacity
NSL4H = NSL 4 mg, High level of buffer capacity

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Body System Preferred Term	NSL4H (N=51) n (%)
SUBJECTS WITH AT LEAST ONE AE	10(19.6)
Eye disorders	0
Blepharitis	0
Gastrointestinal disorders	8(15.7)
Abdominal distension	0
Abdominal pain	0
Abdominal pain upper	0
Cheilitis	0
Diarrhoea	0
Dyspepsia	2(3.9)
Eructation	0
Flatulence	2(3.9)
Nausea	5(9.8)
Saliva altered	1(2.0)
Salivary hypersecretion	0

NSL2L = NSL 2 mg, Low level of buffer capacity
NiQuitinTM 2 mg = NiQuitinTM lozenge 2 mg
NSL4M = NSL 4 mg, Medium level of buffer capacity
NiQuitinTM 4 mg = NiQuitinTM lozenge 4 mg
NSL4L = NSL 4 mg, Low level of buffer capacity
NSL4H = NSL 4 mg, High level of buffer capacity

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Body System Preferred Term	NSL2L (N=101) n (%)	NiQuitinTM 2 mg (N=101) n (%)	NSL4M (N=103) n (%)	NiQuitinTM 4 mg (N=104) n (%)	NSL4L (N=49) n (%)
Gastrointestinal disorders (Continued)					
Stomatitis	0	0	0	1(<1.0)	0
Vomiting	0	0	1(<1.0)	0	0
General disorders and administration site conditions	3(3.0)	0	1(<1.0)	2(1.9)	1(2.0)
Catheter site related reaction	1(<1.0)	0	0	0	0
Chest discomfort	0	0	0	0	1(2.0)
Fatigue	1(<1.0)	0	0	0	0
Pyrexia	1(<1.0)	0	0	1(<1.0)	0
Vaccination site pain	0	0	1(<1.0)	1(<1.0)	0
Infections and infestations	4(4.0)	8(7.9)	10(9.7)	11(10.6)	0
Eye infection	0	0	1(<1.0)	1(<1.0)	0
Genital infection fungal	0	0	0	1(<1.0)	0
Hordeolum	0	0	1(<1.0)	0	0
Nasopharyngitis	4(4.0)	8(7.9)	8(7.8)	9(8.7)	0

NSL2L = NSL 2 mg, Low level of buffer capacity
NiQuitinTM 2 mg = NiQuitinTM lozenge 2 mg
NSL4M = NSL 4 mg, Medium level of buffer capacity
NiQuitinTM 4 mg = NiQuitinTM lozenge 4 mg
NSL4L = NSL 4 mg, Low level of buffer capacity
NSL4H = NSL 4 mg, High level of buffer capacity

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Body System Preferred Term	NSL4H (N=51) n (%)
Gastrointestinal disorders (Continued)	
Stomatitis	0
Vomiting	0
General disorders and administration site conditions	0
Catheter site related reaction	0
Chest discomfort	0
Fatigue	0
Pyrexia	0
Vaccination site pain	0
Infections and infestations	0
Eye infection	0
Genital infection fungal	0
Hordeolum	0
Nasopharyngitis	0

NSL2L = NSL 2 mg, Low level of buffer capacity
NiQuitinTM 2 mg = NiQuitinTM lozenge 2 mg
NSL4M = NSL 4 mg, Medium level of buffer capacity
NiQuitinTM 4 mg = NiQuitinTM lozenge 4 mg
NSL4L = NSL 4 mg, Low level of buffer capacity
NSL4H = NSL 4 mg, High level of buffer capacity

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Subjects with Treatment Related Adverse Events By System Organ Class and Preferred Term:

Table 14.3.1.2 Subjects with Treatment Related Adverse Events By System Organ Class and Preferred Term Subjects in Safety Analysis Set

Body System Preferred Term	NSL2L (N=101) n (%)	NiQuitinTM 2 mg (N=101) n (%)	NSL4M (N=103) n (%)	NiQuitinTM 4 mg (N=104) n (%)	NSL4L (N=49) n (%)
SUBJECTS WITH AT LEAST ONE AE	12(11.9)	7(6.9)	23(22.3)	11(10.6)	12(24.5)
Gastrointestinal disorders	7(6.9)	6(5.9)	14(13.6)	5(4.8)	7(14.3)
Abdominal distension	1(<1.0)	1(<1.0)	1(<1.0)	0	0
Abdominal pain upper	0	0	1(<1.0)	1(<1.0)	0
Cheilitis	1(<1.0)	0	0	0	0
Dyspepsia	2(2.0)	2(2.0)	3(2.9)	0	3(6.1)
Eructation	0	0	0	0	1(2.0)
Flatulence	0	0	1(<1.0)	0	0
Nausea	3(3.0)	3(3.0)	9(8.7)	4(3.8)	4(8.2)
Saliva altered	0	0	0	0	0
Salivary hypersecretion	0	1(<1.0)	2(1.9)	1(<1.0)	0
General disorders and administration site conditions	1(<1.0)	0	0	0	1(2.0)
Chest discomfort	0	0	0	0	1(2.0)
Fatigue	1(<1.0)	0	0	0	0

NSL2L = NSL 2 mg, Low level of buffer capacity
NiQuitinTM 2 mg = NiQuitinTM lozenge 2 mg
NSL4M = NSL 4 mg, Medium level of buffer capacity
NiQuitinTM 4 mg = NiQuitinTM lozenge 4 mg
NSL4L = NSL 4 mg, Low level of buffer capacity
NSL4H = NSL 4 mg, High level of buffer capacity

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Body System Preferred Term	NSL4H (N=51) n (%)
SUBJECTS WITH AT LEAST ONE AE	9(17.6)
Gastrointestinal disorders	7(13.7)
Abdominal distension	0
Abdominal pain upper	0
Cheilitis	0
Dyspepsia	2(3.9)
Eructation	0
Flatulence	1(2.0)
Nausea	4(7.8)
Saliva altered	1(2.0)
Salivary hypersecretion	0
General disorders and administration site conditions	0
Chest discomfort	0
Fatigue	0

NSL2L = NSL 2 mg, Low level of buffer capacity
NiQuitinTM 2 mg = NiQuitinTM lozenge 2 mg
NSL4M = NSL 4 mg, Medium level of buffer capacity
NiQuitinTM 4 mg = NiQuitinTM lozenge 4 mg
NSL4L = NSL 4 mg, Low level of buffer capacity
NSL4H = NSL 4 mg, High level of buffer capacity

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Subjects with Treatment Related Adverse Events By System Organ Class, Preferred Term and Severity:

Table 14.3.1.3 Subjects with Treatment Related Adverse Events By System Organ Class, Preferred Term and Severity Subjects in Safety Analysis Set

Body System Preferred Term	NSL2L (N=101)			NiQuitinTM 2 mg (N=101)		
	Mild n (%)	Mod. n (%)	Sev. n (%)	Mild n (%)	Mod. n (%)	Sev. n (%)
SUBJECTS WITH AT LEAST ONE AE	8(7.9)	4(4.0)	0	4(4.0)	3(3.0)	0
Gastrointestinal disorders	3(3.0)	4(4.0)	0	4(4.0)	2(2.0)	0
Abdominal distension	0	1(<1.0)	0	1(<1.0)	0	0
Abdominal pain upper	0	0	0	0	0	0
Cheilitis	1(<1.0)	0	0	0	0	0
Dyspepsia	0	2(2.0)	0	1(<1.0)	1(<1.0)	0
Eructation	0	0	0	0	0	0
Flatulence	0	0	0	0	0	0
Nausea	2(2.0)	1(<1.0)	0	3(3.0)	0	0
Saliva altered	0	0	0	0	0	0
Salivary hypersecretion	0	0	0	0	1(<1.0)	0
General disorders and administration site conditions	0	1(<1.0)	0	0	0	0
Chest discomfort	0	0	0	0	0	0
Fatigue	0	1(<1.0)	0	0	0	0

NSL2L = NSL 2 mg, Low level of buffer capacity
NiQuitinTM 2 mg = NiQuitinTM lozenge 2 mg
NSL4M = NSL 4 mg, Medium level of buffer capacity
NiQuitinTM 4 mg = NiQuitinTM lozenge 4 mg
NSL4L = NSL 4 mg, Low level of buffer capacity
NSL4H = NSL 4 mg, High level of buffer capacity

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Body System Preferred Term	NSL4M (N=103)			NiQuitinTM 4 mg (N=104)		
	Mild n (%)	Mod. n (%)	Sev. n (%)	Mild n (%)	Mod. n (%)	Sev. n (%)
SUBJECTS WITH AT LEAST ONE AE	16(15.5)	6(5.8)	1(<1.0)	5(4.8)	6(5.8)	0
Gastrointestinal disorders	10(9.7)	3(2.9)	1(<1.0)	0	5(4.8)	0
Abdominal distension	1(<1.0)	0	0	0	0	0
Abdominal pain upper	1(<1.0)	0	0	0	1(<1.0)	0
Cheilitis	0	0	0	0	0	0
Dyspepsia	3(2.9)	0	0	0	0	0
Eructation	0	0	0	0	0	0
Flatulence	0	1(<1.0)	0	0	0	0
Nausea	5(4.9)	3(2.9)	1(<1.0)	0	4(3.8)	0
Saliva altered	0	0	0	0	0	0
Salivary hypersecretion	2(1.9)	0	0	0	1(<1.0)	0
General disorders and administration site conditions	0	0	0	0	0	0
Chest discomfort	0	0	0	0	0	0
Fatigue	0	0	0	0	0	0

NSL2L = NSL 2 mg, Low level of buffer capacity
NiQuitinTM 2 mg = NiQuitinTM lozenge 2 mg
NSL4M = NSL 4 mg, Medium level of buffer capacity
NiQuitinTM 4 mg = NiQuitinTM lozenge 4 mg
NSL4L = NSL 4 mg, Low level of buffer capacity
NSL4H = NSL 4 mg, High level of buffer capacity

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Body System Preferred Term	NSL4L (N=49)			NSL4H (N=51)		
	Mild n (%)	Mod. n (%)	Sev. n (%)	Mild n (%)	Mod. n (%)	Sev. n (%)
SUBJECTS WITH AT LEAST ONE AE	4(8.2)	8(16.3)	0	4(7.8)	5(9.8)	0
Gastrointestinal disorders	1(2.0)	6(12.2)	0	3(5.9)	4(7.8)	0
Abdominal distension	0	0	0	0	0	0
Abdominal pain upper	0	0	0	0	0	0
Cheilitis	0	0	0	0	0	0
Dyspepsia	2(4.1)	1(2.0)	0	1(2.0)	1(2.0)	0
Eructation	0	1(2.0)	0	0	0	0
Flatulence	0	0	0	0	1(2.0)	0
Nausea	0	4(8.2)	0	2(3.9)	2(3.9)	0
Saliva altered	0	0	0	0	1(2.0)	0
Salivary hypersecretion	0	0	0	0	0	0
General disorders and administration site conditions	1(2.0)	0	0	0	0	0
Chest discomfort	1(2.0)	0	0	0	0	0
Fatigue	0	0	0	0	0	0

NSL2L = NSL 2 mg, Low level of buffer capacity
NiQuitinTM 2 mg = NiQuitinTM lozenge 2 mg
NSL4M = NSL 4 mg, Medium level of buffer capacity
NiQuitinTM 4 mg = NiQuitinTM lozenge 4 mg
NSL4L = NSL 4 mg, Low level of buffer capacity
NSL4H = NSL 4 mg, High level of buffer capacity

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/s/

DAVID J LEE
06/01/2018

YUN XU
06/01/2018

Filing Review for Nicorette® Lozenge

SUBMISSION DATES:	February 22, 2018
NDA/SUBMISSION TYPE:	NDA 021-330/S-021PAS (CMC + Labeling)
ACTIVE INGREDIENTS:	Nicotine polacrilex
DOSAGE FORMS:	Lozenge, 2 mg, 4 mg
SPONSOR:	GlaxoSmithKline Consumer Healthcare Julia Kim, Senior Director Regulatory Affairs 184 Liberty Corner Road Warren, NJ 07059 Telephone: 201-957-2392 Fax: 1-908-293-5589 Email: julia.l.kim@gsk.com
REVIEWER:	Brandon McClary, PhD, OND/ODEIV/DNDP
TEAM LEADER:	Kevin Lorick, PhD, RAC OND/ODEIV/DNDP
PROJECT MANAGER:	Alina Salvatore, RPh, MS, RAC OND/ODEIV/DNDP

BACKGROUND:

NDA 021-330/Supplement-021 (S-021), is a prior approval supplement (PAS) with chemistry (CMC) and labeling. S-021 provides for a new formulation for the Nicorette (nicotine polacrilex) line of lozenges for Over-the-Counter (OTC) Nicotine Replacement Therapy (NRT). The proposed lozenge is a coated, mint flavor variant and the size of the proposed lozenge falls in between the original (large) and *mini* Nicorette lozenges currently approved under NDA 021-330 and NDA 022-360, respectively. The proposed indication for the new presentation is identical to the currently approved and marketed Nicorette original (large) and *mini* lozenges; "reduces withdrawal symptoms, including nicotine craving associated with quitting smoking". The proposed lozenge product also consists of different excipients. The Sponsor refers to their new proposed lozenge as Nicorette "Coated Ice Mint" lozenges.

On April 9, 2018, the kick-off meeting was held with input from multiple disciplines regarding the new lozenge formulation. No significant safety issues were identified. However, a potential filing issue was noted:

> The Sponsor currently has approved NDAs for Nicorette Lozenges, NDA 021-330 (Nicorette original large lozenges) and NDA 022-360 (Nicorette *mini* lozenges). The proposed Nicorette "Coated Ice Mint" lozenges are being submitted under an sNDA to the Nicorette Original lozenge (NDA 021-330). Given the separate NDA for the Nicorette mini lozenges, we considered whether this submission should remain a supplement or submitted as a new NDA.

In an FDA Type C meeting held on February 3, 2014, the Sponsor asked if they could submit the new formulation of Nicorette lozenge as a supplement under an existing application. The Sponsor also noted their plans for submission would be at the end of 2014. During the meeting, FDA agreed that a supplement to the existing application (NDA 021-330) would be acceptable. FDA provided additional comments in a post meeting addendum, noting the following:

> "If the new lozenge does not have a different active ingredient, dosage form, route of administration or differ in excipients that require separate clinical studies of safety or effectiveness from the referenced product(s), a supplemental NDA seems appropriate."

The proposed Nicorette "Coated Ice Mint" (mid-size) lozenges will contain the same active ingredient, nicotine polacrilex, and will be available in the same strengths (2 mg and 4 mg) as the currently marketed Nicorette original (large) lozenges (NDA 021-330). Although the proposed lozenges will have a different formulation, shape, size and weight compared to the Nicorette original (large) lozenges, they do not appear to differ in excipients. At this juncture in the review, no separate clinical studies of safety or effectiveness from the referenced product (NDA 021-330) appear to be required. Therefore, this seems to be an adequate filing approach.

Submitted Labeling	Representative of Following SKUs	Date(s) Submitted
20-ct, 2 mg Immediate container "Flip-Pack" (front)	N/A	February 22, 2018
20-ct, 2 mg Immediate container "Flip-Pack" (back)	N/A	February 22, 2018
20-ct, 4 mg Immediate container "Flip Pack" (front)	N/A	February 22, 2018
20-ct, 4 mg Immediate container "Flip-Pack" (back)	N/A	February 22, 2018
20-ct, 2 mg outer carton container backer card (back)	N/A	February 22, 2018
20-ct, 2 mg outer carton container backer card (front)	N/A	February 22, 2018
20-ct, 4 mg outer carton container backer card (back)	N/A	February 22, 2018
20-ct, 4 mg outer carton container backer card (front)	N/A	February 22, 2018
80-ct (4x20 pack), 2 mg outer carton	N/A	February 22, 2018

container backer card (back)		
80-ct (4x20 pack), 2 mg outer carton container backer card (front)	N/A	February 22, 2018
80-ct (4x20 pack), 4 mg outer carton container backer card (back)	N/A	February 22, 2018
80-ct (4x20 pack), 4 mg outer carton container backer card (front)	N/A	February 22, 2018
120-ct (6x20 pack), 2 mg Club pack outer carton container backer card (front and back)	N/A	February 22, 2018
120-ct (6x20 pack), 4 mg Club pack outer carton container backer card (front and back)	N/A	February 22, 2018
Consumer Information leaflet (User's Guide leaflet)	N/A	February 22, 2018

Issues	Yes/No	Comments
Is the supplement correctly assigned as a PA, CBE0, CBE30?	Yes	CMC with labeling
Are the outer container and immediate container labels, and consumer information leaflet and other labeling included for all submitted SKUs?	Yes	
If representative labeling is submitted, does the submitted labeling represent only SKUs of different count sizes (same flavor and dosage form)?	N/A	No representative labeling submitted
Is distributor labeling included?	No	
Does the submission include the annotated specifications for the Drug Facts label?	Yes	
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?	Yes	The Sponsor is proposing the name Nicorette "Coated Ice Mint" lozenges.
Does a medical officer need to review any clinical issues?	No	At this time, there is no clinical information submitted for review. However, may need clinical input based on other disciplines' review.
If SLR, should ONDQA also review?	Yes	PAS is a CMC with labeling which provides for a new formulation and new container closure system proposed (e.g., "Flip pack" container). CMC input is needed.

It is noted that the following additional disciplines are involved with review of this supplement given new formulation proposed:

- ClinPharm
- Biopharm (Sponsor requested waiver of *in vivo* bioequivalence studies for 2 mg lozenge)
- PharmTox (new ingredients)
- Division of Medication Error and Prevention Analysis (DMEPA) (new proprietary name proposed- "Ice Coated Mint")

Review comments: There are no filing issues identified at this time.

The following information requests (IRs) are to be issued:

1. The most recently approved immediate container under this NDA (021-330/Supplement-019) was presented as a POPPAC® vial. However, the inner backer card of the proposed "Ice Coated Mint" labeling presents a different immediate container closure system. Confirm that the container closure system (i.e., "flip-pack") provided in this supplement is a new system.

2. It is unclear if the lozenge image towards the upper right corner of the principal display panel is a true representation of the product. The lozenge image should reflect the true size, color, shape, and imprint (if applicable) of the actual lozenge. Provide a sample of the actual "Ice Coated Mint" lozenge for comparison.

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/s/

BRANDON T MCCLARY
04/13/2018

KEVIN L LORICK
04/19/2018
I concur with the review and recommendations.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-330/S-21

OTHER REVIEW

Draft Labeling Review for Nicorette® Lozenge

SUBMISSION DATES:	February 22, April 18, and June 25, 2018
NDA/SUBMISSION TYPE:	NDA 021-330/S-021; PAS (CMC + Labeling)
ACTIVE INGREDIENTS:	Nicotine polacrilex
DOSAGE FORMS:	Lozenge, 2 mg, 4 mg
SPONSOR:	GlaxoSmithKline Consumer Healthcare Julia Kim, Senior Director Regulatory Affairs 184 Liberty Corner Road Warren, NJ 07059 Telephone: 201-957-2392 Fax: 1-908-293-5589 Email: julia.l.kim@gsk.com
REVIEWER:	Brandon McClary, PhD, OND/ODEIV/DNDP
TEAM LEADER:	Kevin Lorick, PhD, RAC OND/ODEIV/DNDP
PROJECT MANAGER:	Alina Salvatore, RPh, MS, RAC OND/ODEIV/DNDP

I. BACKGROUND

NDA 021-330/Supplement-021 (S-021), is a prior approval supplement (PAS) with updates in chemistry, manufacturing, and controls (CMC) and labeling submitted on February 22, 2018. S-021 provides for a new formulation for the Nicorette (nicotine polacrilex) line of lozenges for Over-the-Counter (OTC) Nicotine Replacement Therapy (NRT). The proposed lozenge is a coated, mint flavor variant and the size of the proposed lozenge falls in between the original (large) and *mini* Nicorette lozenges currently approved under NDA 021-330 and NDA 022-360, respectively. The proposed indication for the new presentation is identical to the currently approved and marketed Nicorette original (large) and *mini* lozenges; "reduces withdrawal symptoms, including nicotine craving associated with quitting smoking". The proposed lozenge product also consists of different excipients. The Sponsor refers to their new proposed lozenge as Nicorette "Coated Ice Mint" lozenges.

It is noted that the following additional disciplines are involved with review of this supplement given the new formulation proposed:

- Clinical Pharmacology (ClinPharm)
- Biopharmaceutics (Biopharm) (b)(4)
- Pharmacology Toxicology (PharmTox) (new ingredients)
- Division of Medication Error and Prevention Analysis (DMEPA) (new proprietary name proposed- "Ice Coated Mint")
- Chemistry, Manufacturing and Controls (CMC) (new formulation and new immediate container closure system)

On April 9, 2018, the kick-off meeting was held with input from multiple disciplines regarding the new lozenge formulation. No significant safety issues were identified. However, a potential filing issue was noted:

> The Sponsor currently has approved NDAs for Nicorette Lozenges, NDA 021-330 (Nicorette original large lozenges) and NDA 022-360 (Nicorette *mini* lozenges). The proposed Nicorette "Coated Ice Mint" lozenges are being submitted under a supplemental NDA to the Nicorette Original lozenge (NDA 021-330). Given the separate NDA for the Nicorette mini lozenges, FDA considered whether this submission should remain a supplement or submitted as a new NDA.

In an FDA Type C meeting held on February 3, 2014, the Sponsor asked if they could submit the new formulation of Nicorette lozenge as a supplement under an existing application. The Sponsor also noted their plans for submission would be at the end of 2014. During the meeting, FDA agreed that a supplement to the existing application (NDA 021-330) would be acceptable. FDA provided additional comments in a post meeting addendum, noting the following:

> "If the new lozenge does not have a different active ingredient, dosage form, route of administration or differ in excipients that require separate clinical studies of safety or effectiveness from the referenced product(s), a supplemental NDA seems appropriate."

The proposed Nicorette "Coated Ice Mint" (mid-size) lozenges will contain the same active ingredient, nicotine polacrilex, and will be available in the same strengths (2 mg and 4 mg) as the currently marketed Nicorette original (large) lozenges (NDA 021-330). Although the proposed lozenges will have a different formulation, shape, size and weight compared to the Nicorette original (large) lozenges, they do not appear to differ in excipients that require separate clinical studies. At this juncture in the review, no separate clinical studies of safety or effectiveness from the referenced product (NDA 021-330) appear to be required. Therefore, this filing approach was adequate.

One April 13, 2018, the following information requests (IRs) were issued to the Sponsor:

1. *"The most recently approved immediate container under this NDA (021-330/Supplement-019) was presented as a POPPAC® vial. However, the inner backer card of the proposed "Ice Coated Mint" labeling presents a different immediate container closure system. Confirm that the container closure system (i.e., "flip-pack") provided in this supplement is a new system."*

On April 18, 2018, the Sponsor confirmed that the proposed immediate container is a new system for the Ice Coated Mint Lozenge. It is different from the POPPAC system, which is the container closure system used for the original Lozenge (NDA 021-330) (See section II. A. c.).

2. *"It is unclear if the lozenge image towards the upper right corner of the principal display panel is a true representation of the product. The lozenge image should reflect the true size, color, shape, and imprint (if applicable) of the actual lozenge. Provide a sample of the actual "Ice Coated Mint" lozenge for comparison."*

   On April 18, 2018, the Sponsor stated that the lozenge image displayed on the upper right corner of the principal display panel is true to size, color and shape when compared to the actual lozenge. The actual lozenge is debossed with "n" on one side and "2" (or "4") on the other side. The Sponsor submitted physical lozenge samples (2 mg and 4 mg). See section II. A. a. iii. for review comments.

On June 5, 2018, a major amendment was submitted. Therefore, the goal date was extended by two months to provide time for a full review of the submission. However, this amendment did not affect labeling that was originally submitted with this supplement.

On June 14, 2018, we issued the following IR to the Sponsor:

3. *"Regarding NDA 21-330/S-021, GSK provided physical lozenge samples (2 mg and 4 mg) by mail on April 18, 2018. GSK confirmed that the actual lozenge is debossed with "n" icon on one side and "2" (or "4") on the other side.* (b)(4)

   (b)(4)

   Note that FDA Guidance, "Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors" issued on April 2013, recommends placing any images of dosage forms at the bottom of the principal display panel label and this image should not compete in size or prominence with the proprietary name and strength information.

   Provide updated labeling for the following:

   20-ct, 2 mg outer carton container backer card (front)
   20-ct, 4 mg outer carton container backer card (front)
   80-ct (4x20 pack), 2 mg outer carton container backer card (front)
   80-ct (4x20 pack), 4 mg outer carton container backer card (front)

120-ct (6x20 pack), 2 mg Club pack outer carton container backer card (front)"
120-ct (6x20 pack), 4 mg Club pack outer carton container backer card (front)

(b)(4)

The Sponsor is proposing to keep the image at the top of the PDP where consumers' view is not obstructed. FDA Guidance, Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors issued on April 2013, recommends placing any images of dosage forms at the bottom of the principal display panel label. However, this is guidance, not regulation. The Sponsor provided justification, noting that if the lozenge image was shifted to the bottom of the PDP, then it will be behind the blister carton and it will be difficult for consumers to clearly see this image. The Sponsor also submitted eye tracking study results which demonstrate that consumers mainly focus on the middle to top section of the PDP.

On July 18, 2018, the following IR was sent to the Sponsor based on recommendations by DMEPA:

4. *As currently presented, the format for the expiration date is not defined on container labels and carton labeling. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format such as MMMYYYY (e.g. JAN2018) or DDMMMYYYY (e.g. 31JAN2018).*

The Sponsor responded on July 25, 2018, confirming that the format for the expiration date will be MMMYYYY.

This labeling reviewed is compared to the mint flavored lozenge labeling submitted in supplement-019 labeling, approved on September 30, 2015.

Submitted Labeling	Representative of Following SKUs	Date(s) Submitted
20-ct, 2 mg Immediate container "Flip-Pack" (front)	N/A	February 22, 2018
20-ct, 4 mg Immediate container "Flip Pack" (front)	N/A	February 22, 2018
20-ct, 2 mg and 4 mg Immediate container "Flip-Pack" (back)	N/A	February 22, 2018
20-ct, 2 mg outer carton container backer card (back)	N/A	February 22, 2018
20-ct, 2 mg outer carton container backer card (front)	N/A	February 22, 2018 and June 25, 2018
20-ct, 4 mg outer carton container backer card (back)	N/A	February 22, 2018
20-ct, 4 mg outer carton container backer	N/A	February 22, 2018 and

card (front)		June 25, 2018
80-ct (4x20 pack), 2 mg outer carton container backer card (back)	N/A	February 22, 2018
80-ct (4x20 pack), 2 mg outer carton container backer card (front)	N/A	February 22, 2018 and June 25, 2018
80-ct (4x20 pack), 4 mg outer carton container backer card (back)	N/A	February 22, 2018
80-ct (4x20 pack), 4 mg outer carton container backer card (front)	N/A	February 22, 2018 and June 25, 2018
120-ct (6x20 pack), 2 mg Club pack outer carton container backer card (front and back)	N/A	February 22, 2018 and June 25, 2018
120-ct (6x20 pack), 4 mg Club pack outer carton container backer card (front and back)	N/A	February 22, 2018 and June 25, 2018
Consumer Information leaflet (User's Guide leaflet)	N/A	February 22, 2018

II. REVIEWERS COMMENTS

A. 20-, 80-, 120-ct, 2 mg and 4 mg Coated Ice Mint lozenge outside container backer card

a. Outer Carton Label Outside Drug Facts

i. The Nicorette Coated Ice Mint Lozenge flavor variant is labelled as "Coated Ice Mint" on the Principal Display Panel (PDP).

Comment: "Coated Ice Mint" is separated from the proprietary name (Nicorette). Therefore, this does not require a new trade name approval (See DMEPA review submitted on April 12, 2018). This is acceptable.

ii. The new background color of the PDP has been updated from green to blue.

Comment: This is acceptable.

iii. A new image of the coated ice mint lozenge is presented towards the upper right corner of the PDP. "NEW" is present directly to the right of the image. In response to our April 13, 2018 information request (see section I. Background IR #2), the Sponsor provided a sample of the actual "Ice Coated Mint" lozenge on April 18, 2018. The actual lozenge is debossed with "n" on one side and "2" (or "4") on the other side. (b)(4)

Compared to the original (large) lozenge, the Coated Ice Mint lozenge is not circular. Instead, it is oval shaped, resembling a tablet dosage form. During internal meetings, there was a concern that this dosage form did not meet the USP definition of a lozenge. There is no USP compendial shape standard for the lozenge dosage form. However, USP 41 defines lozenges as "solid oral dosage forms that are designed to dissolve or disintegrate slowly in the mouth."

Comment: The lozenge image is truthful and not misleading. The dosage form meets the definition of a lozenge per United States Pharmacopeia standards, and the labeling adequately identifies it as such and instructs consumers not to swallow. Therefore, this is acceptable.

b. Outer Carton Drug Facts Label
   i. Warnings
      1. deletion of the "if you are allergic to soya" bullet under the "Do not use" heading.

Comment: Soy protein has been removed from inactive ingredients. Note that "soya" is the British term for soy. The inclusion of the "soya" statement was approved in NDA 021-330/Supplement-18. However, no action is required since this statement is being removed due to the new formulation. This is acceptable.

      2. deletion of the "a sodium-restricted diet" bullet under the "Ask a doctor before use if you have" heading.

Comment: This is removed due to the new formulation (See section II.A.b.iv.1.). This is acceptable.

   ii. Directions
      1. The time that consumer should have the lozenge in their mouth "(20-30 minutes)" has been removed. The Sponsor noted "the oral dissolution time for the Coated Ice Mint lozenge is different from the original lozenge, therefore the dissolution time is not proposed to be added on the label. The Directions

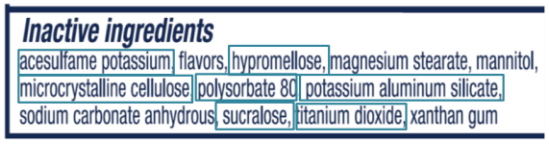
portion of the Drug Facts for the proposed lozenges is however similar to Nicorette Mini Mint lozenge approved drug facts labels which do not include the oral dissolution time."

Comment: This is acceptable. See Clinical Pharmacology Review submitted on June 1, 2018 for further comments.

iii. Inactive Ingredients

1. The inactive ingredients (below) have changed from the previously approved "Original Lozenges".

Proposed NDA 021-330/S-021



Previously approved under NDA 021-330/S-019 (9/30/2015)

Addition: acesulfame potassium, hypromellose, microcrystalline cellulose, polysorbate 80, potassium aluminum silicate, sucralose, titanium dioxide

Deletion: acacia, aspartame, calcium polycarbophil, corn syrup solids, lactose, maltodextrin, potassium bicarbonate, sodium alginate, soy protein, triethyl citrate

Comment: This is acceptable per 21 CFR 201.66(c)(8).

iv. Other Information

1. The statement "each lozenge contains: sodium, 18 mg" has been removed.

Comment: Inactive ingredients have changed (See section II.A.b.iii). Sodium alginate, the only obvious source of sodium, has been removed. Therefore, this is acceptable.

2. The statement "Phenylketonurics: Contains Phenylalanine, 3.4 mg per lozenge)" has been removed.

Comment: Inactive ingredients have changed (See section II.A.b.iii). Aspartame is no longer present as an inactive ingredient. This is acceptable.

3. The statement "keep POPPAC tightly closed and protect from light" has been removed.

Comment: New immediate container closure system has been proposed for the "Coated Ice Mint" lozenges (See Section II.A.c). Based on CMC's assessment (July 19, 2018

email correspondence), stability data provided by the Sponsor indicates that this product is stable for up to 36 months in the proposed container closure system. There is no light sensitive parameter in the specification. The proposed container closure is a blue plastic two piece "Flip-pack", which should provide light protection. Thus, this statement is not required. This is acceptable.

4. The statement "store in the original container" has been added.

Comment: This is acceptable per 21 CFR 201.66(c)(7).

c. 20-ct, 2 mg and 4 mg Immediate Container Label

The most recently approved immediate container under this NDA (021-330/Supplement-019) was presented as a POPPAC® vial. However, the inner backer card of the proposed "Ice Coated Mint" labeling presents a different immediate container closure system. An information request was issued to the Sponsor on April 13, 2018 to confirm if this was indeed a new immediate container closure system.

On April 18, 2018, the Sponsor confirmed that the proposed immediate container is a new system for the Ice Coated Mint Lozenge. It is different from the POPPAC system, which is the container closure system used for the original Lozenge (NDA 021-330).

Comment: This is acceptable. See CMC review submitted for further comments.

d. Consumer Information Leaflet (User's Guide Leaflet)

Currently marketed Nicorette Lozenge products include a booklet version for the User's Guide. However, the proposed User's Guide has been condensed into a two-page leaflet.

The color scheme and overall layout have changed. The following content changes are noted:

Difference in the User's Guide compared to text in current approved Nicorette Lozenges

Section	Statements in the currently marketed Nicorette Original lozenge (NDA 021330)	Proposed Statements for Coated Ice Mint Lozenge
PLANNING YOUR SUCCESS (Point 5)	**Nicorette** Lozenges work best when used together with a support plan. See information to the right for instructions on enrollment in the Committed Quitters Individualized Stop Smoking Program.	**Nicorette** Lozenges work best when used together with a support plan. See information to the right for the MyQuit behavioral support program.
BE PREPARED.	Since smoking is an addiction, it is hard to quit. Even after you stop, there will be times when you WANT a cigarette, sometimes strongly.(See also section on "Challenges To Watch For"). The best defense is to be prepared. Plan now for handling tough times so you don't give in. For example: think about situations when you usually get a craving for cigarettes or where you think you might experience strong cravings. Try to avoid these situations where you can (for example, avoid spending time with smokers, or drinking alcohol, if those things tempt you to smoke). Change your habits. For example, take your coffee break somewhere else. Take a walk. In other words, break the association between your usual habits and cigarettes. If you do encounter a situation where you feel a strong craving, fight it!	Since smoking is an addiction, it is hard to quit. Even after you stop, there will be times when you WANT a cigarette, sometimes strongly (see also section on "**CHALLENGES TO WATCH FOR**"). The best defense is to be prepared. Plan now for handling tough times so you don't give in. Think about situations where you usually get an urge to smoke or where you think you might experience strong urges to smoke (for example, spending time with smokers, or drinking alcohol – try to avoid these situations if those things tempt you to smoke). Change your habits. Take your coffee break somewhere else. Take a walk. Break the association between your usual habits and cigarettes. If you do encounter a situation where you feel a strong urge to smoke, fight it! Take a break from the situation; keep
	Take a break from the situation; keep yourself busy or distracted with other activities. Remind yourself why you want to quit, and above all, remind yourself that having "just one" really will hurt your goal of quitting! To prepare for tough situations, assemble a "survival package"—items that can keep you distracted in case you get a craving. For example, you may include cinnamon gum or hard candy, relaxing music, and things to keep your hands busy like a smooth stone, paper clips, or a rubber ball. Track your progress as you quit. Keep a journal. Write down how many pieces of **Nicorette** Lozenges you use each day. Note if and when you get a craving. If you slip and have a cigarette, don't give up. Stop smoking again and get back on your program with **Nicorette** Lozenges. Establish your support network. Keep friends' and family members' phone numbers ready to get the moral support you need. Before quitting, ask friends and family to support and encourage you. Think of specific ways they can help. Reward yourself. Set aside little gifts to yourself such as a CD or video, which you can earn by overcoming difficult hurdles.	yourself busy or distracted with other activities. Remind yourself why you want to quit, and that having "just one" will really hurt your goal of quitting! Assemble a "survival package"—items that can keep you distracted in case you get an urge to smoke. For example, cinnamon gum or hard candy, relaxing music, things to keep your hands busy like a smooth stone or paper clips, etc. Track your quit progress. Use a journal or the MyQuit App on your mobile phone to note if and when you get an urge to smoke. Note how many pieces of **Nicorette** Lozenges you use each day. If you slip and have a cigarette, don't give up. Stop smoking again and get back on your program with **Nicorette** Lozenges. Establish your support network. Keep friends' and family members' phone numbers ready to get the moral support you need. Before quitting, ask friends and family to support and encourage you. Think of specific ways they can help. Reward yourself. Set aside little gifts to encourage yourself which you can earn by overcoming difficult hurdles.
	FREE INDIVIDUALIZED STOP SMOKING PROGRAM **COMMITTED** **QUITTERS** brought to you by **Nicorette** nicotine polacrilex lozenge **Lozenge** and GSK **? What is COMMITTED QUITTERS** • A FREE, custom-tailored plan to help you break the psychological addiction to smoking. • Throughout your quit attempt, you will receive personalized advice on how to	**MyQuit** Program brought to you by **Nicorette** nicotine polacrilex lozenge **Lozenge** and GSK **Nicorette** has created the **MyQuit** program to provide you with 360° support wherever and whenever you need it. The program provides a network of tools to help you get through those tough moments.
	cope with situations that make you want to smoke. **TO JOIN** **FREE** INDIVIDUALIZED STOP SMOKING PROGRAM **COMMITTED** **QUITTERS** **Enroll online at** **www.committedquitters.com** **or call 1-800-770-0708** **and ask for your *FREE*** **Individualized Stop Smoking Program** • You will be asked a few questions to gain an understanding about you and your specific needs. Trademarks are owned by or licensed to the GSK group of companies. **Call Between 7 am and 12 midnight EST or enroll online 24 hours a day** (ONE PLAN PER CUSTOMER) Read and follow label directions	• **To Your Inbox**: Stay motivated with our personalized email support program that sends encouragement and tips straight to your inbox. • **On The Web**: Get helpful advice, tips and inspiration from ex-smokers on Quit.com. • **On The Go**: Log cravings and track your personal progress on your mobile phone with the MyQuit App. **To learn more visit Quit.com** Trademarks are owned by or licensed to the GSK group of companies.

Comment: This is acceptable.

III. RECOMMENDATIONS

Issue an **APPROVAL** letter to the Sponsor for the submitted Nicorette® Lozenge (nicotine polacrilex, 2 mg, 4 mg) labeling and request final printed labeling. The final printed labeling (FPL) must be identical to the following labeling:

Submitted Labeling	Date(s) Submitted
20-ct, 2 mg Immediate container "Flip-Pack" (front)	February 22, 2018
20-ct, 4 mg Immediate container "Flip Pack" (front)	February 22, 2018
20-ct, 2 mg and 4 mg Immediate container "Flip-Pack" (back)	February 22, 2018
20-ct, 2 mg outer carton container backer card (back)	February 22, 2018
20-ct, 2 mg outer carton container backer card (front)	June 25, 2018
20-ct, 4 mg outer carton container backer card (back)	February 22, 2018
20-ct, 4 mg outer carton container backer card (front)	June 25, 2018
80-ct (4x20 pack), 2 mg outer carton container backer card (back)	February 22, 2018
80-ct (4x20 pack), 2 mg outer carton container backer card (front)	June 25, 2018
80-ct (4x20 pack), 4 mg outer carton container backer card (back)	February 22, 2018
80-ct (4x20 pack), 4 mg outer carton container backer card (front)	June 25, 2018
120-ct (6x20 pack), 2 mg Club pack outer carton container backer card (front and back)	June 25, 2018
120-ct (6x20 pack), 4 mg Club pack outer carton container backer card (front and back)	June 25, 2018
Consumer Information leaflet (User's Guide leaflet)	February 22, 2018

IV. SUBMITTED LABELING

Fifteen (15) pages have been removed as (b)(4), draft labeling, immediately following this page.

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/s/

BRANDON T MCCLARY
07/25/2018

KEVIN L LORICK
07/27/2018
I concur with the review and recommendations.

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	April 12, 2018
Requesting Office or Division:	Division of Nonprescription Drug Products (DNDP)
Application Type and Number:	NDA 021330/S-21
Product Name and Strength:	Nicorette (Nicotine Polacrilex) Lozenges, 2 mg and 4 mg
Product Type:	Single Ingredient Product
Rx or OTC:	OTC
Applicant/Sponsor Name:	GlaxoSmithKline Consumer Healthcare
FDA Received Date:	February 22, 2018
OSE RCM #:	2018-482
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

This review responds to a consult request from DNDP to evaluate the proposed labels and labeling for Nicorette Lozenges to identify areas of vulnerability that may lead to medication errors.

GlaxoSmithKline Consumer Healthcare submitted a Prior Approval Supplement (PAS) for NDA 021330/S-21 seeking approval for a new formulation of Nicorette lozenges on February 22, 2018. The Applicant states the proposed lozenges differ in formulation, coating, size, shape, and weight compared to previously approved Nicorette Lozenges (NDA 021330) and Nicorette Mini Lozenges (NDA 023660).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of materials found the proposed Nicorette container labels and carton labeling may be improved to increase clarity and promote safe use of this product.

4 CONCLUSION & RECOMMENDATIONS

We conclude the proposed container labels and carton labeling for Nicorette Lozenge may be improved to promote the safe use of the product as described in section 4.1.

4.1 RECOMMENDATIONS FOR GLAXOSMITHKLINE CONSUMER HEALTHCARE

A. Container Labels and Carton Labeling

1. As currently presented, the format for the expiration date is not defined on container labels and carton labeling. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format such as MMMYYYY (e.g. JAN2018) or MMMDDYYYY (e.g. JAN312018).

B. Carton Labeling

1. Ensure the lozenge image towards upper right corner of the principal display panel is a true representation of the proposed Nicorette Lozenge. The lozenge image should reflect the true size, color, shape, and imprint (if applicable) of the actual lozenge.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Nicorette Lozenges received on February 22, 2018 from GlaxoSmithKline Consumer Healthcare.

Table 2. Relevant Product Information for Nicorette Lozenge

Initial Approval Date	October 31, 2002
Active Ingredient	Nicotine polacrilex
Indication	Reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking
Route of Administration	Oral
Dosage Form	Troche/Lozenges
Strength	2 mg and 4 mg
Dose and Frequency	If you smoke your first cigarette within 30 minutes of waking up, use 4 mg nicotine lozenge. If you smoke your first cigarette more than 30 minutes after waking up, use 2 mg nicotine lozenge. 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 Do not use more than 5 lozenges in 6 hours. Do not use more than 20 lozenges per day.
How Supplied	The primary packaging is a blue dispenser, referred to as "Flip-Pack" 20 count: One 20 count lozenge primary pack container sealed inside of a form/fill/ seal blister secondary package. 80 count: Four 20 count lozenge primary pack containers sealed inside a form/fill/ seal blister secondary package. 120 count: Six 20 count lozenge primary pack containers sealed inside a form/fill/seal blister secondary package.
Storage	Store at 20°C- 25°C (68°F to 77°F) in the original container
Container Closure	Child resistant

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 3, 2018, we searched DMEPA's previous reviews using the terms, "Nicorette" and "nicotine polacrilex". Our search identified 2 previous reviews,[a,b] and we confirmed that our previous recommendations were implemented or considered.

[a] Oleszczuk, Z. Nicorette Label and Labeling Review (NDA 22360). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2009 APR 8. RCM No: 2009-33.

[b] Oleszczuk, Z. Nicorette Change from Commit Label and Labeling Review (NDA 21330). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2009 OCT 28. RCM No.: 2009-1264.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On April 3, 2018, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community, and Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Nicorette and nicotine

D.2 Results

We retrieved 17 articles, but they were not relevant to this review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Nicorette Lozenge labels and labeling submitted by GlaxoSmithKline Consumer Healthcare.

- Container labels received on February 22, 2018
- Carton labeling received on February 22, 2018
- User's Guide received on February 22, 2018
- Image of physical sample of container labels and carton labeling received on March 29, 2018
- Physical sample of container, container label and carton labeling received on April 4, 2018

G.2 Label and Labeling Images

Only container labels and carton labeling for the proposed 2 mg strength for all counts are shown. See submission for container labels and carton labeling for the proposed 4 mg strength product.

Container labels

(b)(4)

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

COLLEEN L LITTLE
04/12/2018

CHI-MING TU
04/12/2018