

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-066 / S-016

Name: Nicorette (4 mg Nicotine Polacrilex) Gum

Sponsor: GlaxoSmithKline Consumer Healthcare

Approval Date: April 23, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
NDA 20-066 / S-016**

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-066 / S-016

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-066/S-016

GlaxoSmithKline Consumer Healthcare
Attention: Zinatara A. Manji
Associate, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Ms. Manji:

Please refer to your supplemental new drug application dated November 26, 2003, received December 2, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nicorette® (4 mg nicotine polacrilex) gum.

We acknowledge receipt of your submissions dated February 5, 2004, March 1, 2004, March 12, and April 6, 2004.

The April 6, 2004, submission constituted a complete response to our April 2, 2004, action letter.

This supplemental new drug application proposes a new mint flavored uncoated gum.

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

The final printed labeling (FPL) must be identical to the enclosed labeling (carton label submitted April 6, 2004, and Users Guide submitted March 12, 2004) and must be formatted in accordance with the requirements of 21 CFR 201.66.

We remind you to remove the word "New" from the carton label after 6 months of marketing.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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 Laura Shay, Regulatory Project Manager, at (301) 827-2274.

Sincerely yours,

{See appended electronic signature page}

Charles Ganley, MD
Deputy Director
Division of Over the Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Charles Ganley

4/23/04 10:40:29 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-066 / S-016

APPROVABLE LETTER(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-066/S-016

GlaxoSmithKline Consumer Healthcare
Attention: Zinatara A. Manji
Associate, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Ms. Manji:

Please refer to your supplemental new drug application dated November 26, 2003, received December 2, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nicorette® 4 mg (nicotine polacrilex) gum.

We also acknowledge receipt of your February 5, 2004, March 1, 2004, March 12, 2004 and March 29, 2004 submissions.

This supplemental new drug application proposes a new mint flavored uncoated gum.

We have completed the review of this application and it is approvable. Before the application may be approved, however, you must address the following deficiencies:

1. Results from the bioequivalence study provided in this supplement has failed to demonstrate in vivo bioequivalence. Our position is that failure of bioequivalence is due to the difficulties in establishing equivalent chewing patterns between the current and reformulated products as a result of varying amounts of nicotine extracted under the test conditions. Therefore, we recommend using the gum release rate tester ("chewing machine") to test in vitro bioequivalence. An in vitro apparatus such as this can provide both a consistent chewing force and rate of chewing that cannot be achieved readily in vivo and would thus be more reproducible, and allow for the comparison of products in a standardized manner.
2. Submit draft labeling that incorporates the labeling changes provided in the March 12, 2004 amendment.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

At this time, the final specifications for ~~mint~~ mint uncoated Nicorette® 4 mg gum product is acceptable from a pharmacology and toxicology perspective. However, you should _____

_____ to positive genetic toxicology reports in the literature and the potential conversion to nitrosocompounds.

If you have any questions, call Laura Shay, Regulatory Project Manager, at (301) 827-2274.

Sincerely yours,

{See appended electronic signature page}

Charles Ganley, MD

Deputy Director
Division of Over the Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Charles Ganley

4/2/04 03:16:06 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-066 / S-016

APPROVED LABELING



NDA 18-612/S-034
NDA 20-066/S-016

GlaxoSmithKline Consumer Healthcare
Attention: Zinatara A. Manji
Associate, Regulatory Affairs
Parsippany, NJ 07054-3884

Dear Ms. Manji:

We acknowledge receipt of your November 4, 2004, submission containing final printed labeling in response to our April 23, 2004, letters approving your supplemental new drug applications for Nicorette® uncoated (2mg nicotine polacrilex) gum, and Nicorette® uncoated (4mg nicotine polacrilex) gum.

We have reviewed the labeling that you submitted in accordance with our April 23, 2004, letter and we find it acceptable.

In addition, we recommend the following revisions be made at the time of next printing. Submit revised labeling reflecting these changes in the next annual report.

1. Under the subheading "Ask a doctor before use if you have," in the *Warnings* section under Drug Facts, insert the following statement as the first bullet:
 - a sodium-restricted diet
2. In the User Guide, on page 4 under the subheading "Ask a doctor before use if you have," insert the following statement as the first bullet:
 - a sodium-restricted diet
3. Remove the direction "Bite into a piece of Nicorette gum and chew" located on the inside top carton panel. This statement is inconsistent with the directions in Drug Facts and in the user guide.

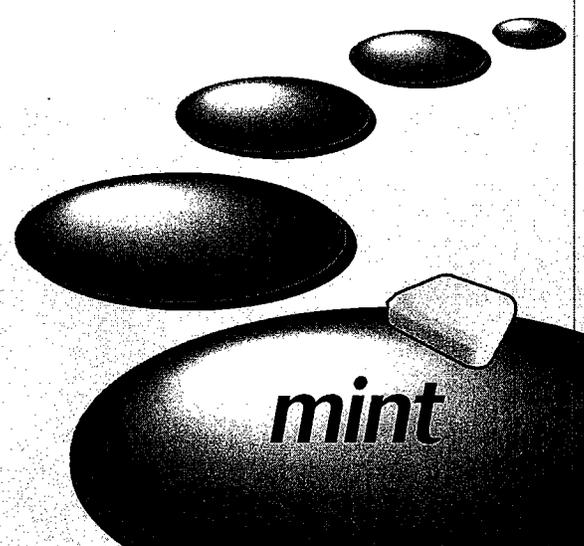
We remind you that the word "NEW" must be deleted from the principal display panel six months after introduction into the OTC market place.

If you have any questions, call Laura Shay, Regulatory Project Manager, at 301-827-2274.

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh M.D., M.P.H.
Deputy Director
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research




Nicorette[®]
nicotine polacrilex gum, 2mg STOP SMOKING AID

2mg
GUM

STARTER KIT
Includes stop smoking plan with
User's Guide and CD

FOR THOSE WHO
SMOKE **LESS THAN**
25 CIGARETTES A DAY
If you smoke 25 or more
cigarettes a day: use Nicorette 4mg

110 PIECES, 2mg EACH

Nicorette 2mg, Soft and Sweet Uncoated Mint, 110 Pieces
Front Panel

Top



To remove the gum, tear off single unit.

Peel off backing, starting at corner with loose edge.

Push gum through foil.

FREE
INDIVIDUALIZED STOP SMOKING PROGRAM
COMMITTED QUITTERS[®]
VISIT COMMITTEDQUITTERS.COM[™]
(To Enroll See Details Inside)

TO INCREASE YOUR SUCCESS IN QUITTING:

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

Bottom



Nicorette[®]
mint

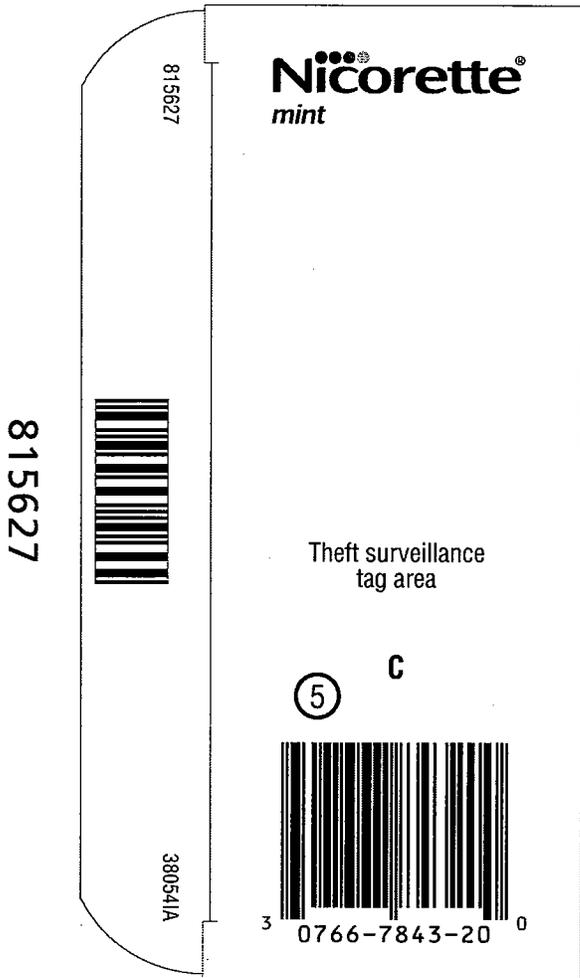
OPEN HERE

Nicorette 2mg, Soft and Sweet Uncoated Mint, 110 Pieces
Top and Bottom Panels

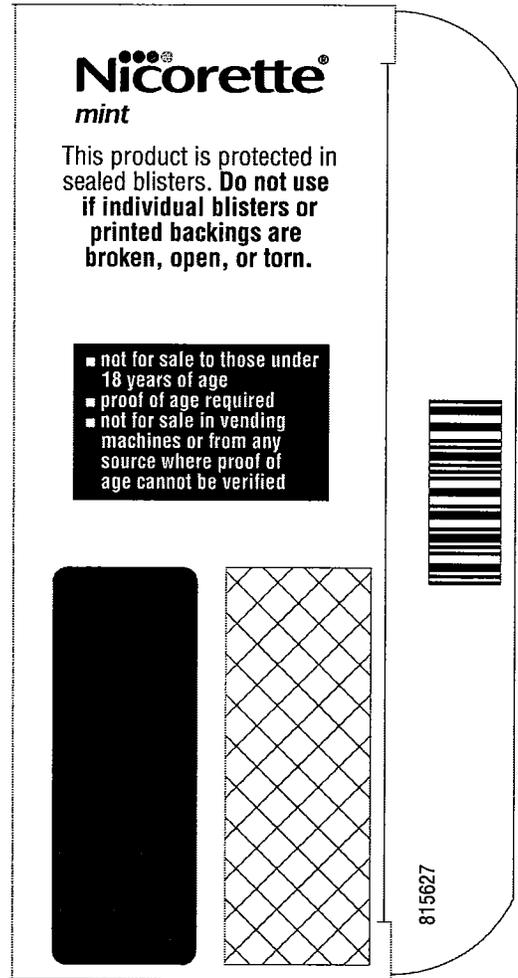
<p>Drug Facts</p> <p>Active ingredient (in each chewing piece) Purpose Nicotine polacrilex (equal to 2mg nicotine).....Stop smoking aid</p> <p>Use</p> <ul style="list-style-type: none"> • reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking <p>Warnings</p> <p>If you 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.</p> <p>Do not use</p> <ul style="list-style-type: none"> • if you continue to smoke, chew tobacco, use snuff, or use a nicotine patch or other nicotine containing products <p>Ask a doctor before use if you have</p> <ul style="list-style-type: none"> • heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate. • high blood pressure not controlled with medication. Nicotine can increase blood pressure. • stomach ulcer or diabetes <p>Ask a doctor or pharmacist before use if you are</p> <ul style="list-style-type: none"> • using a non-nicotine stop smoking drug • taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted. <p>Stop use and ask a doctor if</p> <ul style="list-style-type: none"> • mouth, teeth or jaw problems occur • irregular heartbeat or palpitations occur • you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat <p>Keep out of reach of children and pets. Pieces of nicotine gum may have enough nicotine to make children and pets sick. Wrap used pieces of gum in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away. ▶</p>	<p>Drug Facts (continued)</p> <p>Directions</p> <ul style="list-style-type: none"> • if you are under 18 years of age, ask a doctor before use • before using this product, read the enclosed User's Guide for complete directions and other important information • stop smoking completely when you begin using the gum • if you smoke 25 or more cigarettes a day; use 4mg nicotine gum • if you smoke less than 25 cigarettes a day; use according to the following 12 week schedule: <table border="1" style="width: 100%; border-collapse: collapse; margin: 5px 0;"> <thead> <tr> <th style="padding: 2px;">Weeks 1 to 6</th> <th style="padding: 2px;">Weeks 7 to 9</th> <th style="padding: 2px;">Weeks 10 to 12</th> </tr> </thead> <tbody> <tr> <td style="padding: 2px; text-align: center;">1 piece every 1 to 2 hours</td> <td style="padding: 2px; text-align: center;">1 piece every 2 to 4 hours</td> <td style="padding: 2px; text-align: center;">1 piece every 4 to 8 hours</td> </tr> </tbody> </table> <ul style="list-style-type: none"> • nicotine gum is a medicine and must be used a certain way to get the best results • chew the gum slowly until it tingles. Then park it between your cheek and gum. When the tingle is gone, begin chewing again, until the tingle returns. • repeat this process until most of the tingle is gone (about 30 minutes) • do not eat or drink for 15 minutes before chewing the nicotine gum, or while chewing a piece • to improve your chances of quitting, use at least 9 pieces per day for the first 6 weeks • if you experience strong or frequent cravings, you may use a second piece within the hour. However, do not continuously use one piece after another since this may cause you hiccups, heartburn, nausea or other side effects. • do not use more than 24 pieces a day • it is important to complete treatment. Stop using the nicotine gum at the end of 12 weeks. If you still feel the need to use nicotine gum, talk to your doctor. <p>Other information • store at 20 - 25°C (68 - 77°F)</p> <ul style="list-style-type: none"> • protect from light <p>Inactive ingredients acesulfame potassium, gum base, magnesium oxide, menthol, peppermint oil, sodium bicarbonate, sodium carbonate, xylitol</p> <p>Questions or comments? call 1-800-419-4766 weekdays (10:00 a.m. - 4:30 p.m. EST)</p>	Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12	1 piece every 1 to 2 hours	1 piece every 2 to 4 hours	1 piece every 4 to 8 hours
Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12					
1 piece every 1 to 2 hours	1 piece every 2 to 4 hours	1 piece every 4 to 8 hours					

Manufactured by Pharmacia AB, Stockholm, Sweden for
Glaxo Smith Kline Consumer Healthcare, L.P.
 Moon Township, PA 15108
 © 2004 GlaxoSmithKline

Nicorette 2mg, Soft and Sweet Uncoated Mint, 110 Pieces Back Panel



Right



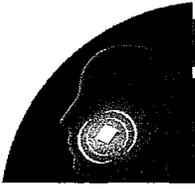
Left

Nicorette 2mg, Soft and Sweet Uncoated Mint, 110 Pieces
Top and Bottom Panels

Bite+Park™

Nicorette isn't like ordinary gum.
It's a medicine and must be used a certain way to get the best results.

Bite



Bite into a piece of Nicorette gum and chew very slowly several times. Stop chewing when you notice a peppery taste, or a slight tingling in your mouth.

Park



Park the Nicorette piece between your cheek and gum, and leave it there. When the peppery taste or tingle is almost gone (in about a minute), start to chew a few times slowly again. When the taste or tingle returns, stop again. Park the piece again (in a different place in your mouth).

Repeat this process until most of the tingle is gone (about 30 minutes).
Read carton and enclosed User's Guide for complete directions and other important information.

©2003 GlaxoSmithKline Read and follow label directions.

IC0121

110ct Inside Copy

NEW
IMPROVED
MINT FLAVOR

Nicorette®

nicotine polacrilex gum, 4mg **STOP SMOKING AID**

4mg
GUM

STARTER KIT
Includes stop smoking plan with
User's Guide and CD

FOR THOSE WHO
SMOKE 25 **OR MORE**
CIGARETTES A DAY
If you smoke *less than* 25
cigarettes a day: use Nicorette 2mg

110 PIECES, 4mg EACH

mint

Nicorette 4mg, Soft and Sweet Mint, 110 Pieces
Front Panel

Top



To remove the gum, tear off single unit.

Peel off backing, starting at corner with loose edge.

Push gum through foil.

FREE
INDIVIDUALIZED STOP SMOKING PROGRAM
COMMITTED QUITTERS[®]
VISIT COMMITTEDQUITTERS.COM
(To Enroll See Details Inside)

TO INCREASE YOUR SUCCESS IN QUITTING:

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

Bottom

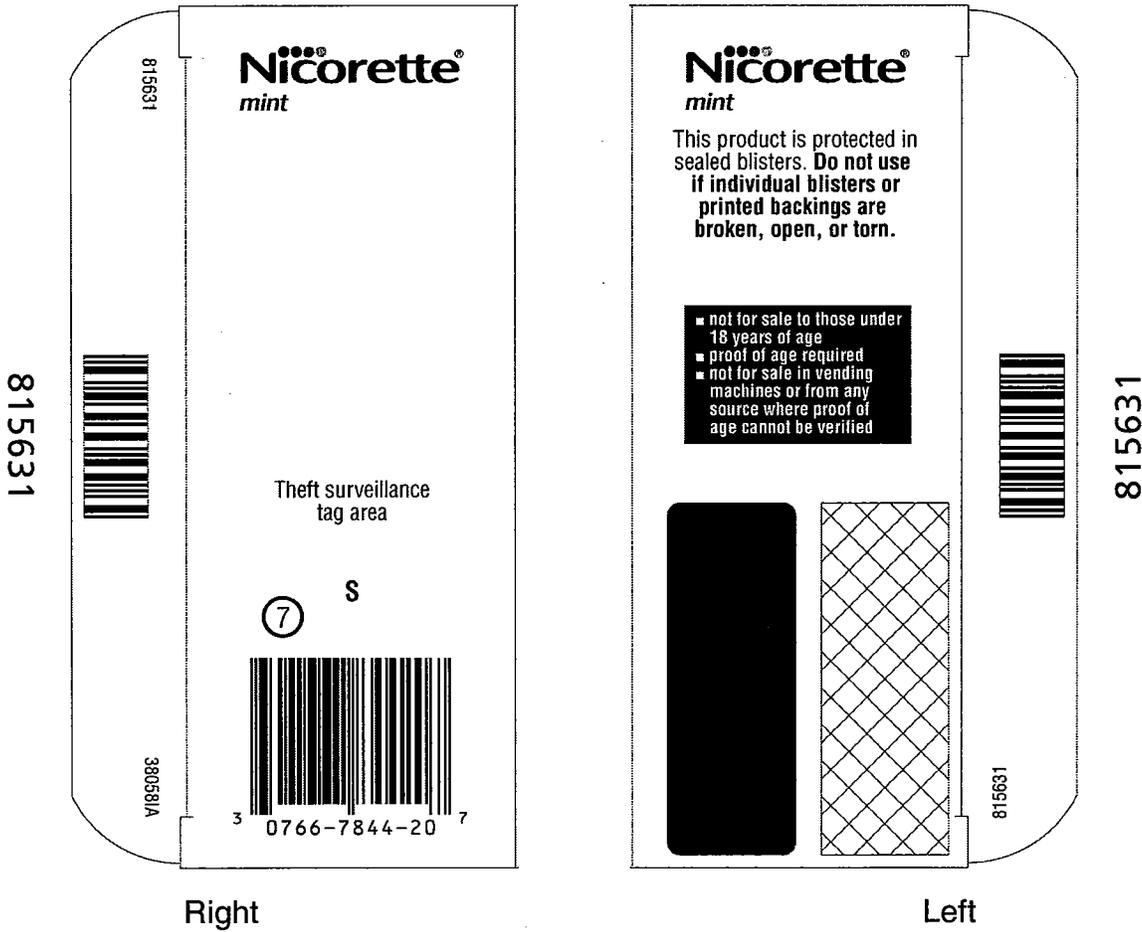


Nicorette 4mg, Soft and Sweet Mint, 110 Pieces
Top and Bottom Panels

<p>Drug Facts</p> <p>Active ingredient (in each chewing piece) Purpose Nicotine polacrilex (equal to 4mg nicotine).....Stop smoking aid</p> <p>Use</p> <ul style="list-style-type: none"> reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking <p>Warnings</p> <p>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.</p> <p>Do not use</p> <ul style="list-style-type: none"> if you continue to smoke, chew tobacco, use snuff, or use a nicotine patch or other nicotine containing products <p>Ask a doctor before use if you have</p> <ul style="list-style-type: none"> heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate. high blood pressure not controlled with medication. Nicotine can increase blood pressure. stomach ulcer or diabetes <p>Ask a doctor or pharmacist before use if you are</p> <ul style="list-style-type: none"> using a non-nicotine stop smoking drug taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted. <p>Stop use and ask a doctor if</p> <ul style="list-style-type: none"> mouth, teeth or jaw problems occur irregular heartbeat or palpitations occur you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat <p>Keep out of reach of children and pets. Pieces of nicotine gum may have enough nicotine to make children and pets sick. Wrap used pieces of gum in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.</p>	<p>Drug Facts (continued)</p> <p>Directions</p> <ul style="list-style-type: none"> if you are under 18 years of age, ask a doctor before use before using this product, read the enclosed User's Guide for complete directions and other important information stop smoking completely when you begin using the gum if you smoke less than 25 cigarettes a day; use 2mg nicotine gum if you smoke 25 or more cigarettes a day; use according to the following 12 week schedule: <table border="1"> <thead> <tr> <th>Weeks 1 to 6</th> <th>Weeks 7 to 9</th> <th>Weeks 10 to 12</th> </tr> </thead> <tbody> <tr> <td>1 piece every 1 to 2 hours</td> <td>1 piece every 2 to 4 hours</td> <td>1 piece every 4 to 8 hours</td> </tr> </tbody> </table> <ul style="list-style-type: none"> nicotine gum is a medicine and must be used a certain way to get the best results chew the gum slowly until it tingles. Then park it between your cheek and gum. When the tingle is gone, begin chewing again, until the tingle returns. repeat this process until most of the tingle is gone (about 30 minutes) do not eat or drink for 15 minutes before chewing the nicotine gum, or while chewing a piece to improve your chances of quitting, use at least 9 pieces per day for the first 6 weeks if you experience strong or frequent cravings, you may use a second piece within the hour. However, do not continuously use one piece after another since this may cause you hiccups, heartburn, nausea or other side effects. do not use more than 24 pieces a day it is important to complete treatment. Stop using the nicotine gum at the end of 12 weeks. If you still feel the need to use nicotine gum, talk to your doctor. <p>Other information - store at 20 - 25°C (68 - 77°F)</p> <ul style="list-style-type: none"> protect from light <p>Inactive ingredients acesulfame potassium, D&C yellow #10 Al. lake, gum base, magnesium oxide, menthol, peppermint oil, sodium carbonate, xylitol</p> <p>Questions or comments? call 1-800-419-4766 weekdays (10:00 a.m. - 4:30 p.m. EST)</p>	Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12	1 piece every 1 to 2 hours	1 piece every 2 to 4 hours	1 piece every 4 to 8 hours
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1 piece every 1 to 2 hours	1 piece every 2 to 4 hours	1 piece every 4 to 8 hours					

Manufactured by Pharmacia AB, Stockholm, Sweden for
GlaxoSmithKline Consumer Healthcare, L.P.
Moon Township, PA 15108
© 2004 GlaxoSmithKline

Nicorette 4mg, Soft and Sweet Mint, 110 Pieces
Back Panel



Nicorette 4mg, Soft and Sweet Mint, 110 Pieces
Side Panels

Bite+Park[™]

Nicorette isn't like ordinary gum.
It's a medicine and must be used a certain way to get the best results.

Bite



Bite into a piece of Nicorette gum and chew very slowly several times. Stop chewing when you notice a peppery taste, or a slight tingling in your mouth.

Park



Park the Nicorette piece between your cheek and gum, and leave it there. When the peppery taste or tingle is almost gone (in about a minute), start to chew a few times slowly again. When the taste or tingle returns, stop again. Park the piece again (in a different place in your mouth).

Repeat this process until most of the tingle is gone (about 30 minutes).
Read carton and enclosed User's Guide for complete directions and other important information.

©2003 GlaxoSmithKline Read and follow label directions.

IC0121

110ct Inside Copy

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/s/

Curtis Rosebraugh
5/10/05 01:24:24 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-066 / S-016

LABELING REVIEW(S)

**Division of OTC Drug Labeling Review
HFD-560**

NDA # 20-066	Sponsor: GlaxoSmithKline
Drug Product: Nicorette — .mint	# of Stock Keeping Units in Submission: 1
Submission Date: April 6, 2004	Review Date: April 21, 2004
Type of Submission: NDA 20066/SCF-016 AZ	Reviewer: Mary S. Robinson

Stock Keeping Unit: Nicorette (nicotine polacrilex) uncoated gum, 4 mg, 110 ct carton

Information Included in the Submission

Content of Submission	Yes	No
1. A cover letter stating that the submission includes new labeling in the Drug Facts format for the drug product and shelf keeping unit(s)	➤	
2. A table of contents or index	➤	
3. The most recent approved labeling *	➤	
4. A representation of the proposed labeling, including any outserts, panel extensions, or other graphical or package techniques intended to be used with the product	➤	
5. Information on formatting, text style, and text size as illustrated in 64 FR 13254 at 293	➤	

*Additional labeling submitted under 21 CFR 314.70(c) or (d) since the last approved labeling should be included in the submission with the date of submission referenced and how they were submitted (e.g. annual report, pending supplement).

The information provided is adequate for review: ➤ Yes

Background

This review is based on GlaxoSmithKline's April 6, 2004 submission of NDA 20066/SCF-016(AZ) for New Mint flavored uncoated Nicorette® 4 mg gum. This submission is in response to the Agency's Approvable Letter, dated April 2, 2004, for the new mint uncoated gum formulation. The submission addresses the deficiencies noted in the Approvable letter. The sponsor has included and highlighted the proposed label changes in draft printed labeling for the carton (see attachment 1). The sponsor states that all labeling revisions will be reflected in final printed labeling for Nicorette — mint Uncoated 2 mg and 4 mg gum. The draft labeling is almost identical to the Mint Nicorette® gum products, with the exception of changes related to flavor. Unless otherwise noted, the reviewer's comments and recommendations refer to the labeling for the new mint flavored uncoated Nicorette® 4 mg, 110ct size carton.

Reviewer's Recommendations

The following recommendations on the proposed labeling can be conveyed to the sponsor. See attachment 1

1. Carton Back, Directions.

- a. Bullet 2. The words "—————" are changed to read: "User's Guide."

This change is acceptable

- b. Bullet 13, first sentence. The sentence "—————" is changed to read:

"it is important to complete treatment. Stop using the nicotine gum at the end of 12 weeks."

This change is acceptable.

Inform the sponsor that the label can be approved.

Mary S. Robinson, M.S.
Regulatory Review Chemist, HFD-560

 4/22/04
Helen Cothran, B.S.
Team Leader, HFD-560

cc: HFD-170:
HFD-560: CGanley/CRosebraugh/HCothran/DShetty/LShay/MRobinson
R/D: MRobinson
F/T: MRobinson

5 page/s of draft
labeling was/were
removed from this portion
of the review

4/21/2004 LABELING REVIEW

20-066 / 5-016

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/s/

Mary Robinson
4/22/04 05:23:51 PM
INTERDISCIPLINARY

Helen Cothran
4/23/04 09:55:14 AM
INTERDISCIPLINARY

Division of OTC Drug Labeling Review
HFD-560

NDA # 20-066	Sponsor: GlaxoSmithKline
Drug Product: Nicorette	# of Stock Keeping Units in Submission: N/A
Submission Date: March 12, 2004	Review Date: March 25, 2004
Type of Submission: NDA 20066/SCF-016 BL	Reviewer: Mary S. Robinson

Stock Keeping Unit: N/A

Information Included in the Submission

Content of Submission	Yes	No
1. A cover letter stating the submission includes new labeling in the Drug Facts format for the drug product and shelf keeping unit(s)	➤	
2. A table of contents or index	➤	
3. The most recent approved labeling *	➤	
4. A representation of the proposed labeling, including any outserts, panel extensions, or other graphical or package techniques intended to be used with the product	➤	

*Additional labeling submitted under 21 CFR 314.70(c) or (d) since the last approved labeling should be included in the submission with the date of submission referenced and how they were submitted (e.g. annual report, pending supplement).

The information provided is adequate for review: ➤ Yes

Background

This review is based on GlaxoSmithKline's March 12, 2004 submissions of NDA 20066/SLR-016 BL for Nicorette® New Mint flavored 4 mg uncoated gum. This submission includes modifications to the User's Guide for the new uncoated Mint gum formulation. The sponsor has included the revised User's Guide in draft printed labeling. (See attachment 1). The User's Guide is almost identical to the User's Guide in the other Mint Nicorette® gum products, with the exception of changes related to flavor and the changes listed below. The sponsor states that the changes to the carton labeling will be reflected in the final printed labeling for this supplement.

Reviewer's Recommendations

The following recommendation on the changes made in the User's Guide can be conveyed to the sponsor. See attachment 1.

1. User's Guide.

- a. The sponsor has moved the heading "TIPS TO MAKE QUITTING EASIER" from before the sentence "STOP USING NICORETTE AT THE END OF WEEK 12" (see page 12) to page 13, bullet 4.

This change is acceptable.

b. Page 13, following bullet 1, the following information is added:

-“Talk to your doctor if you:

- still feel the need to use Nicorette at the end of week 12
- start using Nicorette again after stopping
- start smoking again”

This change is acceptable.

Inform the sponsor that the above changes to the user's guide are acceptable.

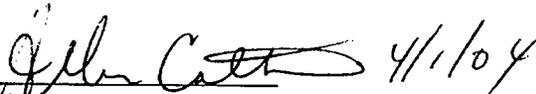
The sponsor did not submit carton labeling in this amendment # 3, but stated that the changes to the carton labeling submitted in NDA 20066/S-017 will be reflected in the final printed labeling for this supplement (S-016).

Remind the sponsor that the carton label change recommended for NDA 20066/S-017 is as follows:

On the carton back, under directions revise bullet 13, first sentence " _____
_____ to read:

“it is important to complete treatment. Stop using the nicotine gum at the end of 12 weeks.”

Mary S. Robinson, M.S.
Regulatory Review Chemist, HFD-560


Helen Cothran, B.S.
Team Leader, HFD-560

cc: HFD-170:
HFD-560: CGanley/CRosebraugh/HCothran/DShetty/LShay/MRobinson
R/D: MRobinson
F/T/: MRobinson

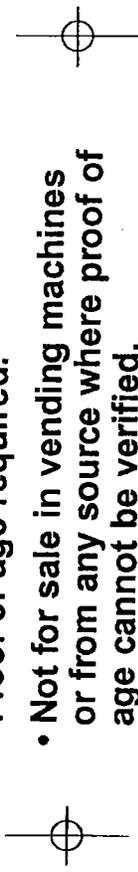
Nicorette

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

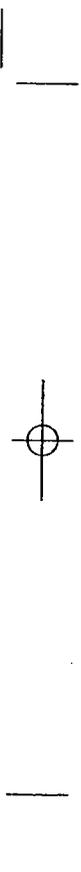
**HOW TO USE
NICORETTE
TO HELP YOU
QUIT SMOKING.**

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- 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.



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KEYS TO SUCCESS.

- 1) You must really want to quit smoking for Nicorette® to help you.
- 2) You can greatly increase your chances for success by using at least 9 to 12 pieces every day when you start using Nicorette. See page 11.
- 3) You should continue to use Nicorette as explained in this User's Guide for 12 full weeks.
- 4) Nicorette works best when used together with a support program — See page 3 for details.
- 5) If you have trouble using Nicorette, ask your doctor or pharmacist or call GlaxoSmithKline at 1-800-419-4766 weekdays (10:00 am - 4:30 pm EST).

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**SO YOU
DECIDED
TO QUIT.**

That's why you've made the right choice in choosing Nicorette gum. Your own chances of quitting smoking depend on how much you want to quit, how strongly you are addicted to tobacco, and how closely you follow a quitting

program like the one that comes with Nicorette.

**QUITTING
SMOKING
IS HARD!**

If you've tried to quit before and haven't succeeded, don't be discouraged! Quitting isn't easy. It takes time, and most people try a few times before they are successful. The important thing is to try again until you succeed.

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This User's Guide will give you support as you become a non-smoker. It will answer common questions about Nicorette and give tips to help you stop smoking, and should be referred to often.

WHERE TO GET HELP. You are more likely to stop smoking by using Nicorette with a support program that helps you break your smoking habit. 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 Wallet Card on the back cover of this User's Guide. If you find you cannot stop smoking or if you start smoking again after using Nicorette, remember breaking this addiction doesn't happen overnight. You may want to talk to a health care professional who can help you improve your chances of quitting the next time you try Nicorette or another method.

LET'S GET ORGANIZED. Your reason for quitting may be a combination of concerns about health, the effect of smoking on your appearance, and pressure from your family and friends to stop smoking. Or maybe you're

concerned about the dangerous effect of second-hand smoke on the people you care about.

All of these are good reasons. You probably have others. Decide your most important reasons, and write them down on the wallet card inside the back cover of this User's Guide. Carry this card with you. In difficult moments, when you want to smoke, the card will remind you why you are quitting.

WHAT YOU'RE UP AGAINST. Smoking is addictive in two ways. You need for nicotine has become both physical and mental. You must overcome both addictions to stop smoking. So while Nicorette will lessen your

body's physical addiction to nicotine, you've got to want to quit smoking to overcome the mental dependence on cigarettes. Once you've decided that you're going to quit, it's time to get started. But first, there are some important warnings you should consider.

SOME 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.

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This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

Do not use

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

Ask a doctor before use if you have

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

Ask a doctor or pharmacist before use if you are

- using a non-nicotine stop

smoking drug

- taking a prescription medicine for depression or asthma. Your prescription dose may need to be adjusted.

Stop use and ask a doctor if

- mouth, teeth or jaw problems occur
- irregular heartbeat or palpitations occur
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat

Keep out of reach of children and

pets. Pieces of nicotine gum may have enough nicotine to make children and pets sick. Wrap used pieces of gum in paper and throw away in the trash. In case of

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

LET'S GET STARTED. Becoming a non-smoker starts today. First, check that you bought the right starting dose. If you smoke 25 or more cigarettes a day, use 4 mg nicotine gum. If you smoke less than 25 cigarettes a day, use 2 mg nicotine gum. Next, read through the entire User's Guide carefully. Then, set your personalized quitting schedule. Take out a calendar that you can use to track your progress, and identify four dates, using the stickers in the center of this User's Guide:

STEP 1. (Weeks 1-6). Your quit date (and the day you'll start using Nicorette gum).

Choose your quit date (it should be soon). This is the day you will quit smoking cigarettes entirely and begin using Nicorette to satisfy your cravings for nicotine. For the first six weeks, you'll use a piece of Nicorette every hour or two. Be sure to follow the directions starting on pages 9 and 11. Place the Step 1 stickers on this date.

STEP 2. (Weeks 7 to 9). The day you'll start reducing your use of Nicorette.

After six weeks, you'll begin gradually reducing your Nicorette usage to one piece every two to four hours. Place the Step 2

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sticker on this date (the first day of week seven).

STEP 3. (Weeks 10-12). The day you'll further reduce your use of Nicorette.

Nine weeks after you begin using Nicorette, you will further reduce your nicotine intake by using one piece every four to eight hours.

Place the Step 3 sticker on this date (the first day of week ten). For the next three weeks, you'll use a piece of Nicorette every four to eight hours.

End of treatment: The day you'll complete Nicorette therapy. Nicorette should not be used for longer than twelve weeks. Identify the date thirteen weeks after the date you chose in Step 1, and

place the "EX-SMOKER" sticker on your calendar.

PLAN AHEAD. Because smoking is an addiction, it is not easy to stop. After

you've given up cigarettes, you will still have a strong urge to smoke. Plan ahead NOW for these times, so you're not defeated in a moment of weakness. The following tips may help:

- Keep the phone numbers of supportive friends and family members handy.
- Keep a record of your quitting process. Track the number of Nicorette pieces you use each day, and whether you feel a craving for cigarettes. In the event that you slip, immediately stop smoking and resume your

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quit attempt with the Nicorette program.

- Put together an Emergency Kit that includes items that will help take your mind off occasional urges to smoke. Include cinnamon gum or lemon drops to suck on, a relaxing cassette tape, and something for your hands to play with, like a smooth rock, rubber band, or small metal balls.
- Set aside some small rewards, like a new magazine or a gift certificate from your favorite store, which you'll "give" yourself after passing difficult hurdles.
- Think now about the times when you most often want a

cigarette, and then plan what else you might do instead of smoking. For instance, you might plan to take your coffee break in a new location, or take a walk right after dinner, so you won't be tempted to smoke.

**HOW Nicorette's
NICORETTE~~™~~
GUM WORKS.** pieces

provide nicotine to your system — they work as a temporary aid to help you quit smoking by reducing nicotine withdrawal symptoms. Nicorette provides a lower level of nicotine to your blood than cigarettes, and allows you to gradually do away with your body's need for nicotine.

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Because Nicorette does not contain the tar or carbon monoxide of cigarette smoke, it does not have the same health dangers as tobacco. However, it still delivers nicotine, the addictive part of cigarette smoke. Nicotine can cause side effects such as headache, nausea, upset stomach, and dizziness.

HOW TO USE If you are under 18 years of age, ask a doctor before use.

Before you can use Nicorette correctly, you have to practice! That sounds silly, but it isn't. Nicorette isn't like ordinary chewing gum. It's a medicine, and must be chewed a certain way to

work right. Chewed like ordinary gum, Nicorette won't work well and can cause side effects. An overdose can occur if you chew more than one piece of Nicorette at the same time, or if you chew many pieces one after another. Read all the following instructions before using Nicorette. Refer to them often to make sure you're using Nicorette gum correctly. If you chew too fast, or do not chew correctly, you may get hiccups, heartburn, or other stomach problems. Don't eat or drink for 15 minutes before using Nicorette, or while chewing a piece. The effectiveness of Nicorette may be reduced by some foods and drinks, such as coffee, juices, wine or soft drinks.

- 1) Stop smoking completely before you start using Nicorette.
 - 2) To reduce craving and other withdrawal symptoms, use Nicorette according to the dosage schedule on page 11.
 - 3) Chew each Nicorette piece ~~very slowly several times.~~
 - 4) Stop chewing when you notice a peppery taste, or a slight tingling in your mouth. (This usually happens after about 15 chews, but may vary from person to person.)
 - 5) "PARK" the Nicorette piece between your cheek and gum, and leave it there.
 - 6) When the peppery taste or tingle is almost gone (in about
- 
- 

a minute), start to chew a few times slowly again. When the taste or tingle returns, stop again.

7) Park the Nicorette piece again (in a different place in your mouth).

8) Repeat steps 3 to 7 (chew, chew, park) until most of the nicotine is gone from the Nicorette piece (usually happens in about half an hour; the peppery taste or tingle won't return.)

9) Wrap the used Nicorette piece in paper and throw away in the trash.

PLACE THESE STICKERS ON YOUR CALENDAR:



AT THE BEGINNING OF WEEK #1
(QUIT DATE)



AT THE BEGINNING OF WEEK #7



AT THE BEGINNING OF WEEK #10



12 WEEKS AFTER QUIT DATE

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The following chart lists the recommended usage schedule for Nicorette:

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

DO NOT USE MORE THAN 24 PIECES PER DAY.

To improve your chances of quitting, use at least 9 pieces of Nicorette a day, if you experience strong or frequent cravings, you may use a second piece within the hour. However, do not continuously use one piece after another, since this may cause you hiccups, heartburn, nausea or other side effects.

HOW TO REDUCE YOUR NICORETTE USAGE. The goal of using Nicorette is to slowly reduce your dependence on nicotine. The schedule for using Nicorette will help you reduce your nicotine craving gradually as you reduce and then stop your use of Nicorette. Here are some tips to help you cut back during each step and then stop using Nicorette:

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- After a while, start chewing each Nicorette piece for only 10 to 15 minutes, instead of half an hour. Then, gradually begin to reduce the number of pieces used.
- Or, try chewing each piece for longer than half an hour, but reduce the number of pieces you use each day.
- Substitute ordinary chewing gum for some of the Nicorette pieces you would normally use. Increase the number of pieces of ordinary gum as you cut back on the Nicorette pieces.
- Check how well you've reduced your daily usage of Nicorette in Weeks 10 to 12. You should only be using about

3 to 5 pieces a day. Get ready to stop.

STOP USING NICORETTE AT THE END OF WEEK 12. The following tips may help you with stopping Nicorette Gum at the end of 12 weeks.

- Set a stop date.
- Use the same number of pieces of confectionery gum or mints as you were using Nicorette per day. At the times when you have an urge to use Nicorette, use a strong flavored gum or mint such as cinnamon or peppermint.

- Reduce the number of pieces of gum or mints you use by one piece per day until you do not need to use any gum or mints.
 - Talk to your doctor if you:
 - still feel the need to use Nicorette at the end of week 12
 - start using Nicorette again after stopping
 - start smoking again
- TIPS TO MAKE QUITTING EASIER**
- Within the first few weeks of giving up smoking, you may be tempted to smoke for pleasure, particularly after completing a difficult task, or at a party or bar. Here are some tips to help get you through the important first stages of becoming a non-smoker:
- On Your Quit Date:**
- Ask your family, friends and co-workers to support you in your efforts to stop smoking.
 - Throw away all your cigarettes, matches, lighters, ashtrays, etc.
 - Keep busy on your quit day.
 - Exercise. Go to a movie. Take a walk. Get together with friends.
 - Figure out how much money you'll save by not smoking. Most ex-smokers can save more than \$1,000 a year.
 - Write down what you will do with the money you save.
 - Know your high risk situations and plan ahead how you will deal with them.

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- Keep Nicorette gum near your bed, so you'll be prepared for any nicotine cravings when you wake up in the morning.
 - Visit your dentist and have your teeth cleaned to get rid of the tobacco stains.
- Right after Quitting:**
- During the first few days after you've stopped smoking, spend as much time as possible at places where smoking is not allowed.
 - Drink large quantities of water and fruit juices.
 - Try to avoid alcohol, coffee and other beverages you associate with smoking.



- Remember that temporary urges to smoke will pass, even if you don't smoke a cigarette.
- Keep your hands busy with something like a pencil or a paper clip.
- Find other activities which help you relax without cigarettes.
- Swim, jog, take a walk, play basketball.
- Don't worry too much about gaining weight. Watch what

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you eat, take time for daily exercise, and change your eating habits if you need to.

- Laughier helps. Watch or read something funny.

WHAT TO EXPECT.

Your body is now coming back into balance. During the first few days after you stop smoking, you might feel *rogy* and nervous and have trouble concentrating. You might get headaches, feel dizzy and a little out of sorts, feel *sweaty* or have stomach upsets. You might even have trouble sleeping at first. These are typical withdrawal symptoms that will go away with time. Your smoker's cough will

get worse before it gets better. But don't worry, that's a good sign. Coughing helps clear the tar deposits out of your lungs.



After A Week Or Two.

By now you should be feeling more confident that you can handle those smoking urges. Many of your withdrawal symptoms have left by now, and you should be noticing some positive signs: less coughing, better breathing and an improved sense of taste and smell, to name a few.

After A Month.

You probably have the urge to smoke much less often now. But urges may still occur, and when they do, they are likely to be powerful ones that come out of nowhere. Don't let them catch you off guard. Plan ahead for these difficult times.

Concentrate on the ways non-smokers are more attractive than smokers. Their skin is less likely to wrinkle. Their teeth are whiter, cleaner. Their breath is fresher. Their hair and clothes smell better. That cough that seems to make even a laugh sound more like a rattle is a thing of the past. Their children and others around them are healthier, too.

What To Do About Relapse.

What should you do if you slip and start smoking again? The answer is simple. A lapse of one or two or even a few cigarettes has not spoiled your effort! Discard your cigarettes, forgive yourself and try again.

If you start smoking again, keep your box of **Nicorette** for your next quit attempt.

If you have taken up regular smoking again, don't be discouraged. Research shows that the best thing you can do is to try again. The important thing is to learn from your last attempt.

- Admit that you've slipped, but don't treat yourself as a failure.
- Try to identify the "trigger" that

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caused you to slip, and prepare a better plan for dealing with this problem next time.

- Talk positively to yourself – tell yourself that you have learned something from this experience.
- Make sure you used Nicorette gum correctly over the full 12 weeks to reduce your craving for nicotine.
- Remember that it takes practice to do anything, and quitting smoking is no exception.

WHEN THE STRUGGLE IS OVER.

Once you've stopped smoking, take a second and pat yourself on your back. Now do it again. You deserve it.

Remember now why you decided to stop smoking in the first place. Look at your list of reasons. Read them again. And smile.

Now think about all the money you are saving and what you'll do with it. All the non-smoking places you can go, and what you might do there. All those years you may have added to your life, and what you'll do with them. Remember that temptation may not be gone forever. However, the hard part is behind you so look forward with a positive attitude, and enjoy your new life as a non-smoker.

QUESTIONS & ANSWERS.

1. How will I feel when I stop smoking and start using Nicorette? You'll need to prepare yourself for some nicotine withdrawal symptoms. These begin almost immediately after you stop smoking, and are usually at their worst during the first three or four days. Understand that any of the following is possible:

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

Nicorette can help provide relief from withdrawal symptoms such as irritability and nervousness, as well as the craving for nicotine you used to satisfy by having a cigarette.

2. Is Nicorette just substituting one form of nicotine for another?

Nicorette does contain nicotine. The purpose of Nicorette is to provide you with enough nicotine to help control the physical withdrawal symptoms so you can deal with the mental aspects of quitting. During the 12 week program, you will gradually reduce your nicotine intake by switching to fewer pieces each day. Remember, don't use Nicorette together with nicotine

patches or other nicotine containing products.

3. Can I be hurt by using Nicorette?

For most adults, the amount of nicotine in the gum is less than from smoking. Some people will be sensitive to even this amount of nicotine and should not use this product without advice from their doctor (see page 4). Because Nicorette is a gum-based product, chewing it can cause dental fillings to loosen and aggravate other mouth, tooth and jaw problems. Nicorette can also cause hiccups, heartburn and other stomach problems especially if chewed too quickly or not chewed correctly.

4. Will I gain weight?

Many people do tend to gain a few pounds the first 6-10 weeks after they stop smoking. This is a very small price to pay for the enormous gains that you will make in your overall health and attractiveness. If you continue to gain weight after the first two months, try to analyze what you're doing differently. Reduce your fat intake, choose healthy snacks, and increase your physical activity to burn off the extra calories.

5. Is Nicorette more expensive than smoking?

The total cost of Nicorette for the twelve week program is about equal to what a person who smokes one and a half packs of

cigarettes a day would spend on cigarettes for the same period of time. Also, use of Nicorette is only a short-term cost, while the cost of smoking is a long-term cost, because of the health problems smoking causes.

6. What if I slip up?

Discard your cigarettes, forgive yourself and then get back on track. Don't consider yourself a failure or punish yourself. In fact, people who have already tried to quit are more likely to be successful the next time.



GOOD LUCK!

Recommended dosage schedule for Nicorette:

STEP 1
weeks 1 to 6 1 piece every 1 to 2 hours
STEP 2
weeks 7 to 9 1 piece every 2 to 4 hours
STEP 3
weeks 10 to 12 1 piece every 4 to 8 hours

WALLET CARD

**My most important reasons
to quit smoking are:**

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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

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/s/

Mary Robinson
4/1/04 10:59:48 AM
INTERDISCIPLINARY

Helen Cothran
4/1/04 12:32:21 PM
INTERDISCIPLINARY

Division of OTC Drug Labeling Review
HFD-560

NDA # 20-066	Sponsor: GlaxoSmithKline
Drug Product: Nicorette	# of Stock Keeping Units in Submission: 4
Submission Date: November 26, 2003 and February 5, 2004	Review Date: March 2, 2004
Type of Submission: NDA 20066/SCF-016 and NDA 20066/SCF -016BL	Reviewer: Mary S. Robinson

Stock Keeping Unit: Nicorette (nicotine polacrilex) uncoated gum, 4 mg, _____ 110 ct carton, _____

Information Included in the Submission

Content of Submission	Yes	No
1. A cover letter stating that the submission includes new labeling in the Drug Facts format for the drug product and shelf keeping unit(s)	➤	
2. A table of contents or index	➤	
3. The most recent approved labeling *	➤	
4. A representation of the proposed labeling, including any outserts, panel extensions, or other graphical or package techniques intended to be used with the product	➤	
5. Information on formatting, text style, and text size as illustrated in 64 FR 13254 at 293	➤	

*Additional labeling submitted under 21 CFR 314.70(c) or (d) since the last approved labeling should be included in the submission with the date of submission referenced and how they were submitted (e.g. annual report, pending supplement).

The information provided is adequate for review: ➤ Yes

Background

This review is based on GlaxoSmithKline's November 26, 2003 and February 5, 2004 submissions of NDA 20066/SCF-016 for Nicorette® New Mint flavored 4 mg uncoated gum. These submissions introduce the new uncoated Mint gum formulation and contain proposed modifications to the current Nicorette® Mint drug product labeling for the carton and User's Guide. The sponsor has included the proposed label changes in full color draft printed labeling for the Cartons and User Guide (see attachment 1). The labeling is almost identical to the Mint Nicorette® gum products, with the exception of changes related to flavor and the changes listed below. Unless otherwise noted, the reviewer's comments and recommendations refer to the labeling for the mint flavored uncoated Nicorette® 4 mg _____ 110ct, _____, size cartons, CD cover, CD label and CD transcript (in February 5, 2004 submission), Blister, User's Guide and inside top panel.

Reviewer's Recommendations

The following recommendations on the proposed labeling can be conveyed to the sponsor. See attachment 1

1. **Carton Back, Directions.**
 - a. Bullet 13, first sentence. "_____"

For emphasis, make two sentences as follows:

"it is important to complete treatment. Stop using the nicotine gum at the end of 12 weeks."

2. User's Guide.

Under "STOP USING NICORETTE AT THE END OF WEEK 12," bullet 4, page 13, the following information is added:

-Talk to your doctor if you still feel the need to use Nicorette, _____
_____ start smoking again.

This tip is long and confusing. For clarity, break it into shorter phrases as follows:

-Talk to your doctor if you:

- still feel the need to use Nicorette at the end of week 12
- start using Nicorette again after stopping
- start smoking again"

3. Delete the word "New" from the label after the first 6 months of OTC marketing.

Inform the sponsor that the label cannot be approved until the changes noted above are made.

Mary S. Robinson, M.S.
Regulatory Review Chemist, HFD-560

 3/30/04
Helen Cothran, B.S.
Team Leader, HFD-560

cc: HFD-170:
HFD-560: CGanley/CRosebraugh/HCothran/DShetty/LShay/MRobinson
R/D: MRobinson
F/T: MRobinson

40 page/s of draft
labeling was/were
removed from this portion
of the review

3/2/2004 LABELING REVIEW

20-066 / S-016

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

/s/

Mary Robinson
4/1/04 09:56:10 AM
INTERDISCIPLINARY

Helen Cothran
4/1/04 12:30:27 PM
INTERDISCIPLINARY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-066 / S-016

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS
REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

Nicotine Polacrilex 2 and 4mg gum
NDA 18-612 SCF-034 (2mg)
NDA 20-066 SCF-016 (4mg)
Nicorette Uncoated Gum
Reviewer: E.D. Bashaw, Pharm.D.

Glaxo SmithKline
Parsippany, NJ

Submission Date:
11/26/03
2/24/04

Review of In Vitro Release Data/Flavor Change

Background

These supplements have been submitted to allow for both a change in flavor of Nicorette gum from citrus to mint, and to allow for both coated and un-coated forms of the mint flavor.

Previously this sponsor had submitted the results of in vivo bioequivalency studies for comparison of these products to the currently marketed Nicorette® gum. When the bioequivalence criteria were not met, the Sponsor had tried to adjust the data for the remaining nicotine and had recalculated the 95% confidence intervals for comparison of the products. This approach for determining bioequivalence was considered not acceptable, and the Agency recommended that the sponsor provide an in vitro comparison of the products by using an apparatus also known as the “chewing machine”. An in vitro apparatus such as this can provide standardized conditions such as consistent chewing force and rate of chewing, and allow a more reliable in vitro comparison of these products. In vitro data collected in this manner complement in vivo comparison of these products.

This sponsor had developed previously a “chewing machine” in which six independent sets of metal teeth could be set at pre-determined rates to maintain a fixed amount of force to chew medicated gums in separate water baths. The water baths then would be sampled over time for release testing purposes. The results plotted over time can be analyzed for similarity by graphical methods as well as by application of the F2 testing approach as described in the FDA Guidance on Immediate Release Solid Oral Dosage Forms.

Methods

In these studies, nicotine release profiles were determined from the original Nicorette (currently marketed) product (2- and 4-mg) and the New Mint flavored coated and uncoated products (2- and 4-mg). A total of 6 individual gums from 3 batches of each of the test and reference formulations were evaluated. The instrumental settings (chewing frequency, jaw distance, temperature) and testing media were identical for all

formulations. Samples were withdrawn from the cells after 2, 5, 10, 20 and 30 minutes of mastication.

Lots Tested

Test

Nicorette 2mg Mint flavored (also referred to as S&S)* uncoated batches:
DB 616, DB 617, DB 618
Nicorette 4mg Mint flavored (also referred to as S&S) uncoated batches:
DD 705, DD 706, DD 707

Nicorette 2mg Mint flavored (also referred to as S&S) coated batches:
EE 8001, EE 8002, EE 8003
Nicorette 4mg Mint flavored (also referred to as S&S) coated batches:
EE 8102, EE8103, EE 8105

**[Note that Nicorette New Mint was referred to as "S&S" in previous development work.]*

Reference

Nicorette 2mg Orange (also referred to as citrus) batches: DD 560, DD 561, DD 562
Nicorette 4mg Orange (also referred to as citrus) batches: BK623A, DA533A, DD 585A

The in vitro release profiles, as determined in the "chewing" apparatus, were also compared by the f2 (similarity factor) approach that is described in the FDA CDER Guidance for Immediate Release Solid Oral Dosage forms. Following application of the f2 approach, values greater than 50 are considered to be indicative of similar profiles.

Results

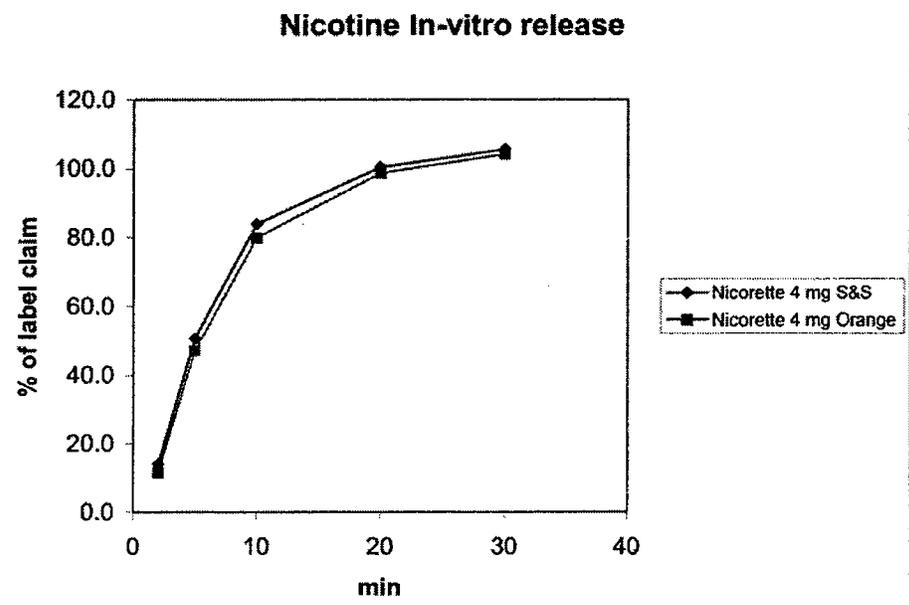
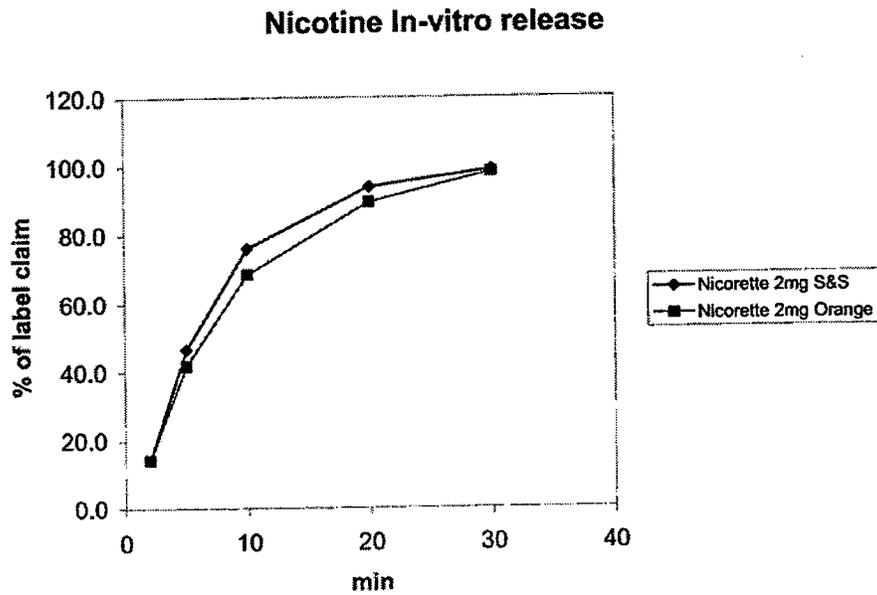
Overall the results from in vitro testing of different lots of Nicorette gum gave reproducible results across both strengths and coatings of the gum. Over a 30 min test period the "chewing" apparatus/machine was able to extract out, on average, approximately 99% of the labeled amount of nicotine (see tables 1-4, attached). In terms of F2 testing, the following mean results were obtained:

Comparator	F2 factor relative to reference product
2mg uncoated	67
4mg uncoated	66
2mg coated	65
4mg coated	74

In vitro nicotine release profiles for the proposed Nicorette formulations and the currently marketed product are similar. For illustration purposes, profiles for the proposed 2- and 4-mg mint flavored uncoated Nicorette product are presented in this

review and the in vitro release data for both coated and uncoated proposed Nicorette products and the currently marketed Nicorette product are presented in the attached Tables 1-4.

Mean Nicotine Release Rates 2 and 4mg uncoated gum



Conclusions

The results of the F2 testing along with a visual examination of the data reveal that the change in flavor or the coating of the products have had little if any effect on the release of nicotine from the polacrilex matrix that is the Nicorette gum. These data complement the in vivo data submitted earlier and support that the proposed products are similar to the currently marketed Nicorette gum.

Recommendation

Based on the information presented in this supplement, the Division of Pharmaceutical Evaluation-III has no objection to the proposed formulation changes/line extensions for a mint flavored coated and a mint flavored uncoated 2 and 4 mg Nicorette product.

Dennis Bashaw, Pharm.D.
HFD-540/550/560
PK Review Team Leader

Secondary Review: Arzu Selen, Ph.D., Deputy Director, DPE-III _____

**APPEARS THIS WAY
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TABLE 1

Table 1. The compiled nicotine in-vitro release results from three batches of the test gum Nicorette 2 mg S&S and three batches of the reference gum Nicorette 2 mg Orange.

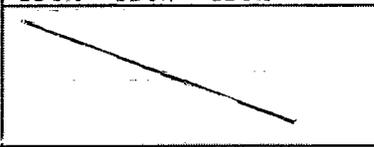
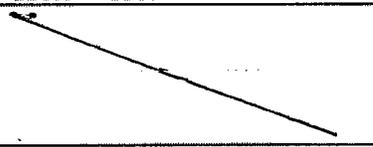
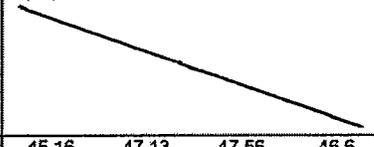
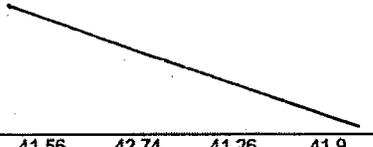
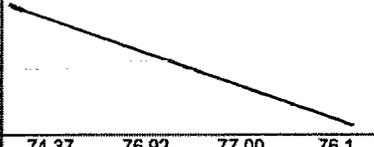
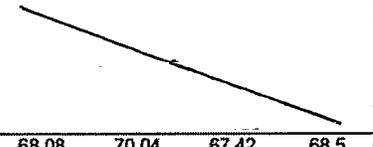
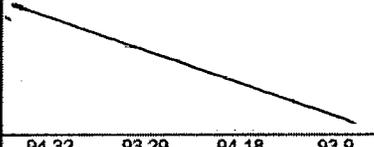
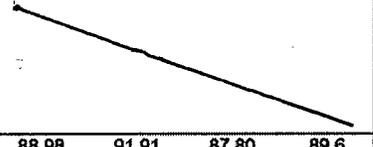
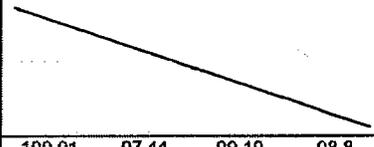
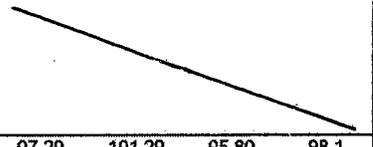
Time (min)	Study No: A02228				Study No: A02177			
	Nicorette 2mg S&S				Nicorette 2mg Orange			
	(% of label claim)				(% of label claim)			
	DB 616	DB 617	DB 618		DD560	DD561	DD562	
2								
Average	13.79	14.70	14.56	14.4	13.90	14.89	13.96	14.2
SD	1	2	2		1	1	1	
RSD	10	10	12		7	10	7	
5								
Average	45.16	47.13	47.56	46.6	41.56	42.74	41.26	41.9
SD	4	3	3		3	2	3	
RSD	8	6	6		7	6	6	
10								
Average	74.37	76.92	77.00	76.1	68.08	70.04	67.42	68.5
SD	5	4	2		3	1	3	
RSD	7	5	3		4	2	5	
20								
Average	94.32	93.29	94.18	93.9	88.98	91.91	87.80	89.6
SD	3	2	2		3	2	5	
RSD	3	3	2		4	2	5	
30								
Average	100.01	97.44	99.10	98.8	97.29	101.29	95.80	98.1
SD	2	2	2		5	3	4	
RSD	2	2	2		5	3	4	

TABLE 2

Table 1. The compiled nicotine in-vitro release results from three batches of the test gum Nicorette 2 mg S&S coated and three batches of the reference gum Nicorette 2 mg Orange/Citrus

Time (min)	Study No: A03277 Nicorette 2 mg S&S coated (% of label claim)				Study No: A02177 Nicorette 2 mg Orange/Citrus (% of label claim)				
	EE8001	EE8002	EE8003		DD560	DD561	DD562		
2									
	Average SD RSD	15.31 2 11	15.41 2 11	15.12 1 10	15.3	13.90 1 7	14.89 1 10	13.96 1 7	14.2
5									
	Average SD RSD	45.67 2 3	47.20 3 7	47.60 2 4	46.8	41.56 3 7	42.74 2 6	41.26 3 6	41.9
10									
	Average SD RSD	73.68 2 3	74.12 3 5	76.59 1 2	74.8	68.08 3 4	70.04 1 2	67.42 3 5	68.5
20									
	Average SD RSD	92.88 1 1	92.22 4 4	94.99 2 2	93.4	88.98 3 4	91.91 2 2	87.80 5 5	89.6
30									
	Average SD RSD	100.47 1 1	98.54 4 4	100.55 2 2	99.9	97.29 5 5	101.29 3 3	95.80 4 4	98.1

TABLE 3

Table 2. The compiled nicotine in-vitro release results from three batches of the test gum Nicorette 4 mg S&S and three batches of the reference gum Nicorette 4 mg Orange.

Time (min)	Study No: A02376 Nicorette 4mg S&S (% of label claim)				Study No: A02376 Nicorette 4mg Orange (% of label claim)			
	DD705	DD706	DD707	14.0	DA533A	BK623A	DD585A	11.5
	2							
Average	17.12	13.67	11.22	14.0	11.80	11.72	10.85	11.5
SD	1	0	0		1	1	0	
RSD	8	3	4		9	10	3	
5								
Average	56.65	48.73	47.29	50.9	47.34	50.06	44.24	47.2
SD	3	3	1		2	2	2	
RSD	4	6	2		4	3	4	
10								
Average	87.73	82.01	81.95	83.9	79.31	82.98	77.47	79.9
SD	3	3	2		3	2	2	
RSD	3	4	2		3	2	2	
20								
Average	102.61	99.38	99.21	100.4	95.88	102.71	97.30	98.6
SD	2	3	3		4	2	2	
RSD	2	3	3		4	2	2	
30								
Average	106.67	104.65	105.32	105.5	101.24	108.06	103.15	104.1
SD	1	4	2		2	2	2	
RSD	1	4	2		2	2	2	

TABLE 4

Table 2. The compiled nicotine in-vitro release results from three batches of the test gum Nicorette 4 mg S&S coated and three batches of the reference gum Nicorette 4 mg Orange/Citrus.

Time (min)	Study No: A03277 Nicorette 4 mg S&S coated (% of label claim)				Study No: A02376 Nicorette 4 mg Orange/Citrus (% of label claim)				
	EE8102	EE8103	EE8105		DA533A	BK623A	DD585A		
2									
	Average SD RSD	16.98 1 6	16.31 2 13	16.49 1 9	16.6	11.80 1 9	11.72 1 10	10.85 0 3	11.5
5									
	Average SD RSD	53.41 3 5	53.02 4 8	55.87 4 7	54.1	47.34 2 4	50.06 2 3	44.24 2 4	47.2
10									
	Average SD RSD	82.55 3 3	82.86 3 4	85.84 4 5	83.7	79.31 3 3	82.98 2 2	77.47 2 2	79.9
20									
	Average SD RSD	98.37 2 2	99.19 2 2	99.98 3 3	99.2	95.88 4 4	102.71 2 2	97.30 2 2	98.6
30									
	Average SD RSD	104.05 1 1	104.55 2 2	105.10 2 2	104.6	101.24 2 2	108.06 2 2	103.15 2 2	104.1

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this page is the manifestation of the electronic signature.**

/s/

Dennis Bashaw
4/22/04 06:59:48 PM
BIOPHARMACEUTICS

Arzu Selen
4/22/04 07:12:03 PM
BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Review

Nicotine Polacrilex Gum

Glaxo Smith Kline

Nicorette®

Reviewer: E.D. Bashaw, Pharm.D.

Submission Date:

NDA 18-612 s-034 & -037, 2mg

11/26/03

NDA 20-066 s-016 & -019, 4mg

2/20/04

Review of NDA Supplement

Background

This review covers two NDAs and a total of four supplements divided between the 2mg nicotine gum (NDA 18-612 s-034 & -037) and the 4mg nicotine gum (NDA 20-066 s-016 & -019). Specifically these supplements deal with a minor reformulation issue, namely the addition of mint flavoring and an outer coating. The sponsor had been advised previously that an in vitro study would be possible under the provisions of 21CFR320.22(d)(4), however, the sponsor elected to perform two in vivo biostudies instead. As the 2 and 4mg nicotine gums are under separate NDAs, the results from these trials were filed separately as a supplement to each NDA.

NDA 18-612 S-034 (2mg)

NDA 20-066 S-016 (4mg)

These supplemental New Drug Applications (sNDA) are being submitted to acquire Over-the-Counter (OTC) marketing approval for a new mint flavor Nicorette (nicotine polacrilex) 2 and 4 mg gum. This new formulation is also referred to by the sponsor as: Nicorette — mint Uncoated 2 and 4 mg gum, throughout this application.

An *in vivo* bioequivalence study (Study No. NICSOS-9132-003) entitled, “*Bioequivalence between Two New Nicotine Gums (2 and 4 mg) and Nicorette® Gum (2 and 4 mg) in an Open, Randomized, Crossover, Phase I Study in Healthy Smoking Volunteers*” was included in these supplements. This study was designed to assess the bioequivalence between the original flavor 2 mg gum and the new mint flavor 2 mg variant, which is the subject of this sNDA. The study also compares the 4 mg original flavor gum and the 4 mg new mint flavor variant.

NDA 18-612 S-037 (2mg)

NDA 20-066 S-019 (4mg)

These supplemental New Drug Applications (SNDA) are being submitted to acquire Over-the-Counter (OTC) marketing approval for a mint flavor Nicorette (nicotine polacrilex) 2 and 4 mg **coated** gum. This new formulation is also referred to by the sponsor as: Nicorette — mint Coated 2 and 4 mg gum throughout this application. The drug product contained in this supplemental application utilizes the original uncoated gum formulation as the gum core of the drug product. A xylitol-based

hard coating was applied to the uncoated gum to _____

One *in vivo* bioequivalence study (Study No. NICSOS-9132-005) entitled, “Bioequivalence between Two New Nicotine Gums (2 and 4 mg) and Nicorette® Gum (2 and 4 mg) in an Open, Randomized, Crossover, Phase I Study in Healthy Smoking Volunteers” was included in this supplement. This study was designed to assess the bioequivalence between the original flavor 2 mg gum and the new mint flavor 2 mg coated variant, which is the subject of this sNDA. The study also compares the 4 mg original flavor gum and the 4 mg new mint flavor coated variant.

Overview of the Studies

Both of these studies used the same general design, in the appendix, the relevant summary pharmacokinetic parameters are reproduced in the following table for the uncoated 2mg gum:

NICSOS-9132-003

Pharmacokinetic parameters (mean ± SD, median, min - max) – 2 mg gum

Formulation	Dose (mg)	C _{max} ¹ (ng/ml)	t _{max} ¹ (h)	AUC _{0-12h} ¹ (h*ng/ml)	Peak/trough ¹ (%)	Swing ¹ (%)
New nicotine gum (n=30)	1.48 ± 0.18	18.1 ± 5.9	0.52 ± 0.10	16.6 ± 5.4	18 ± 6	20 ± 8
	1.50 (0.85-1.81)	17.9 (6.4 – 33.6)	0.50 (0.33 – 0.67)	16.7 (5.6 – 29.9)	17 (7 – 31)	18 (7 – 37)
Nicorette [®] gum (n=29)	1.32 ± 0.17	15.4 ± 5.2	0.44 ± 0.13	14.2 ± 4.7	17 ± 7	19 ± 8
	1.32 (0.86-1.61)	15.6 (6.5 – 30.1)	0.50 (0.17 – 0.67)	14.7 (6.0 – 25.5)	17 (6 – 33)	18 (6 – 38)

1) last dosing interval

The equivalent data for the uncoated 4mg product is reproduced below;

NICSOS-9132-003

Pharmacokinetic parameters (mean ± SD, median, min - max) – 4 mg gum

Formulation	Dose (mg)	C _{max} (ng/ml)	t _{max} (h)	AUC _{0-4h} (h*ng/ml)	AUC _{0-24h} (h*ng/ml)	t _{1/2} (h)
New nicotine gum (n=30)	3.05 ± 0.38	9.8 ± 2.7	0.67 ± 0.27	26.1 ± 8.1	31.7 ± 10.0	2.77 ± 0.83
	3.13 (1.90-3.74)	9.2 (5.9 – 17.7)	0.50 (0.33 – 1.25)	24.9 (11.8 – 46.4)	29.4 (15.8 – 59.8)	2.90 (1.33 – 4.18)
Nicorette [®] gum (n=31)	2.87 ± 0.30	8.4 ± 2.5	0.64 ± 0.23	22.7 ± 8.8	28.7 ± 11.1	2.85 ± 0.89
	2.87 (2.20-3.39)	7.9 (4.9 – 17.7)	0.50 (0.33 – 1.00)	22.4 (10.2 – 54.0)	27.0 (12.7 – 70.6)	2.88 (1.34 – 4.95)

While the data is fairly comparable within dose strengths, the variability in the amount of nicotine extracted ranges from _____ mg. These values barely approach the labeled 4mg amount, suggesting that, the extraction of nicotine from either dosage strength is less than the labeled amount and is dependent upon the physical act of chewing.

In a likewise manner the bioavailability data from the -005 study is reproduced below:

NICSOS-9132-005 (Coated Gum)

Pharmacokinetic parameters (mean ± SD, median, min - max) – 2 mg gum						
Formulation	Dose ¹ (mg)	C _{max,11-12h} (ng/ml)	t _{max} ² (h)	AUC _{11-12h} (h*ng/ml)	Peak/trough ² (%)	Swing ² (%)
New nicotine gum (n=22)	1.40 ± 0.23	14.3 ± 3.6	0.55 ± 0.16	12.9 ± 3.4	23 ± 9	27 ± 12
	1.40 (0.82-1.72)	14.2 (8.1 – 21.9)	0.50 (0.3 – 0.8)	12.9 (6.9 – 20.4)	23 (6 – 42)	26 (6 – 57)
Nicorette® gum (n= 22)	1.26 ± 0.21	12.6 ± 3.1	0.45 ± 0.11	11.4 ± 2.9	20 ± 8	23 ± 10
	1.25 (0.69-1.63)	12.0 (6.2 – 18.3)	0.50 (0.2 – 0.7)	11.2 (5.2 – 17.1)	18 (9 – 38)	20 (9 – 48)

1) n=27 2) last dosing interval

NICSOS-9132-005 Coated Gum)

Pharmacokinetic parameters (mean ± SD, median, min - max) – 4 mg gum						
Formulation	Dose ¹ (mg)	C _{max} (ng/ml)	t _{max} (h)	AUC ₁ (h*ng/ml)	AUC _∞ (h*ng/ml)	t _{1/2} (h)
New nicotine gum (n=24)	3.01 ± 0.36	9.6 ± 3.0	0.78 ± 0.29	31.0 ± 11.0	31.6 ± 9.8	2.53 ± 0.72
	3.02 (2.01-3.66)	9.7 (4.9 – 15.9)	0.75 (0.3 – 1.5)	30.0 (12.8 – 49.4)	31.0 (16.4 – 47.1)	2.67 (1.2 – 4.2)
Nicorette® gum (n=24)	2.85 ± 0.31	8.4 ± 2.4	0.66 ± 0.21	28.6 ± 9.9	29.1 ± 8.5	2.84 ± 1.20
	2.87 (2.11-3.38)	8.1 (5.4 – 16.2)	0.75 (0.3 – 1.0)	29.1 (11.2 – 54.1)	28.0 (12.7 – 50.8)	2.76 (1.2 – 6.1)

1) n=30

Bioequivalence

In order to demonstrate bioequivalence between the two formulations and two strengths, the sponsor conducted in vivo bioequivalence trials in healthy adult smokers. From the collected pk data 90% confidence intervals were constructed for assessment of bioequivalence between the products and within strengths.

	NICSOS-9132-003		NICSOS-9132-005	
	UNCOATED		COATED	
	2mg	4mg	2mg	4mg
AUCt		1.13-1.29*		0.96-1.19
AUCinf		1.10-1.23		0.98-1.17
Cmax	1.12-1.22	1.12-1.28*	1.08-1.21	1.03-1.25
AUC (MD)**	1.11-1.22		1.07-1.19	

*Exceeds 90% C.I. acceptance criteria of 80-125%

** AUC (MD)-Area Under the Curve Multiple Dose (last dosing interval)

In the “003” trial the 4mg product was outside the acceptable bioequivalence range for both AUC and Cmax. To address this issue the sponsor has proposed an alternative

analysis based on the actual delivered doses of nicotine, determined from residual gum analysis.

Residual Nicotine Analysis

One of the difficulties in doing bioequivalency trials with gum products is that dose is dependent upon the force and rate of chewing. In a crossover trial the amount of drug released can vary significantly. In order to correct for this the sponsor collected the chewed gum from this trial and did an extraction to determine the residual amount of nicotine released by chewing. The results of the residual analysis for this trial “-003” are contained in the table below:

Table 4. Amount of nicotine (mg) released during chewing

Treatment	Dose #	Mean	SD	Median	Range
2 mg New nicotine gum	1	1.47	0.18	1.51	/
2 mg New nicotine gum	12	1.48	0.18	1.50	
2 mg Nicorette® gum	1	1.30	0.18	1.33	
2 mg Nicorette® gum	12	1.33	0.17	1.35	
4 mg New nicotine gum	1	3.05	0.38	3.13	
4 mg Nicorette® gum	1	2.87	0.30	2.87	

From the collected gum from this trial one can see that the mean and median difference (current formulation – new formulation) in the extracted amount of nicotine was 0.18mg and 0.26mg respectively.

Although a numerically small difference, the sponsor then took this data and recalculated the pk parameters based on the actual delivered amounts of nicotine, and constructed new 90% confidence intervals.

90% Confidence Intervals based on
Residual Nicotine Analysis

	NICSOS-9132-003	
	2mg	4mg
AUCt		1.07-1.21
AUCinf		1.04-1.15
Cmax	1.01-1.10	1.06-1.20
AUC (MD)	1.01-1.10	

This “dose delivered correction” is an unusual way of assessing relative bioavailability and bioequivalence. However, most dosage forms, ie. tablets, capsules, suspensions, etc. are not dependent on direct physical action on the dosage form for drug release. That is drug release is normally a passive process and not an active one. In the past because of this variability in drug release the Agency has encouraged the sponsor to use the “chewing machine” as a release rate tester. This is an automated device that, similar to a dissolution apparatus, has a number of stations submerged in a suitable media that

simulates the chewing action of teeth with porcelain disks. While not a direct simulation of the mouth and chewing per se, it does share similarities with in vitro dissolution apparatuses in that it is reproducible and can be calibrated as to speed and force.

Given the difficulties in obtaining re-producible release characteristics, as seen in these studies, it is the Agency's opinion that in vivo bioequivalency testing is not the preferred mechanism for approval of these minor formulation changes. Instead the Agency recommends that repeat testing with the in vitro chewing machine be used as it can provide reproducible conditions (i.e. control over the force and rate of chewing) that cannot be achieved in vivo.

Recommendation

Because of the results of the in vivo biostudies, the Agency has a split recommendation:

NDA 18-612 S-037 (2mg) and NDA 20-066 S-019 (4mg)-these supplements for the mint flavored coated nicotine gum are acceptable from a Clinical Pharmacology/Biopharmaceutics standpoint as they were able to establish in vivo bioequivalence between the current and re-formulated products.

NDA 18-612 S-034 (2mg) and NDA 20-066 S-016 (4mg)-these supplements for the mint flavored uncoated nicotine gum are not acceptable as the sponsor has failed to demonstrate in vivo bioequivalence, which is the only comparative data submitted for this product. It is the Agency's position that this failure of bioequivalence is due to the difficulties in establishing equivalent chewing patterns between the current and re-formulated products as a result of varying amounts of nicotine extracted under the test conditions. Rather than requiring a new in vivo biostudy, the Agency recommends that the sponsor demonstrate in vitro bioequivalence using the gum release rate tester, otherwise known as the "chewing machine". An in vitro apparatus such as this can provide both a consistent chewing force and rate of chewing that cannot be achieved readily in vivo and would thus be more reproducible, and allow for the comparison of products in a standardized manner.

Dennis Bashaw, Pharm.D.
PK Review Team Leader
for HFD-540/550/560
DPE-III (HFD-880)

Secondary Review: Arzu Selen, Ph.D., Deputy Director, DPE-III _____

Study # NICSOS-9132-003

Study Title: *Bioequivalence Between Two New Nicotine Gums (2 and 4 mg) and Nicorette® Gum (2 and 4 mg) In an Open, Randomized, Crossover, Phase I Study in Healthy Smoking Volunteers*

Objectives: This study was designed to assess the bioequivalence between the original flavor 2 mg gum and the new mint flavor 2 mg variant, under multiple dose conditions. The study also compares the 4 mg original flavor gum and the 4 mg new mint flavor variant following a single dose..

Study Design: Open-label, single dose (4 mg) and multiple-dose (2 mg), 2x2-way, randomized, cross-over study in healthy adult smokers.

Treatments:

Drug	Form	Strength	Appearance	Size
New nicotine gum	Chewing gum	4 mg	square, uncoloured	14 x 14 x 5 mm
New nicotine gum	Chewing gum	2 mg	square, uncoloured	14 x 14 x 5 mm
Nicorette® nicotine gum	Chewing gum	4 mg	square, yellow	14 x 14 x 5 mm
Nicorette® nicotine gum	Chewing gum	2 mg	square, uncoloured	14 x 14 x 5 mm

Procedures

A total of 32 healthy smokers (17 male, 15 female) were enrolled in the study. One subject withdrew before start of study. Three subjects withdrew for reasons not related to the study after the third session. One subject was excluded from the analysis due to nicotine baseline concentration >5 ng/ml. Thus 30 subjects on 4 mg (single-dose comparison) and 28 subjects on 2 mg (multipledose comparison) were analyzed.

Twelve repeated doses (1 hour apart) of either new mint or original flavor were administered for the 2 mg gum and one dose of either new mint or original flavor for the 4 mg gum. Upon completion of each phase the subjects were washed out for a week before being crossed over to the other treatment.

Blood sampling for determination of nicotine were drawn pre-dose and at 5, 10, 15, 20, 30, 45 minutes, 1, 1.25 (1 hour 15 minutes), 1.5, 2, 3, 4, 6, 8 and 10 hours after administration of treatments A and B. The sampling times after treatments C and D were before each dose and at 10, 20, 30, 40, 50 minutes and 1 hour after the last administration. The exact time points for sampling were recorded. Time deviations of 1 minute or more from the planned sampling time were recorded.

The blood samples (5 ml) were collected in heparinized tubes. The plasma was then separated by centrifugation at 1000g for 10 minutes at +4°C. The plasma was then transported, in frozen condition (-20°) to Analytical R&D, Pharmacia AB, Consumer Healthcare, Helsingborg, Sweden., where they were analyzed for nicotine and cotinine (the primary metabolite of nicotine).

Results

Pharmacokinetic parameters (mean \pm SD, median, min - max) . 2 mg gum

Formulation	Dose (mg)	C _{max} (ng/ml) ¹	t _{max} (h) ¹	AUC _{0-12h} (h ² ng/ml) ¹	Peak ¹ trough ¹ (%)	Swing ¹ (%)
New nicotine gum (n=30)	1.46 \pm 0.16	18.1 \pm 5.9	0.52 \pm 0.10	16.6 \pm 5.4	18 \pm 6	20 \pm 8
	1.50	17.9	0.50	16.7	17	18
	(0.85-1.81)	(8.4 - 33.6)	(0.33 - 0.67)	(5.6 - 29.9)	(7 - 31)	(7 - 37)
Nicorette gum (n= 29)	1.32 \pm 0.17	15.4 \pm 5.2	0.44 \pm 0.13	14.2 \pm 4.7	17 \pm 7	19 \pm 8
	1.32	15.6	0.50	14.7	17	18
	(0.86-1.81)	(6.5 - 30.1)	(0.17 - 0.67)	(6.0 - 25.5)	(8 - 33)	(8 - 38)

¹last dosing interval

Figure 4. Mean nicotine plasma concentrations after once hourly administration of 2 mg gums

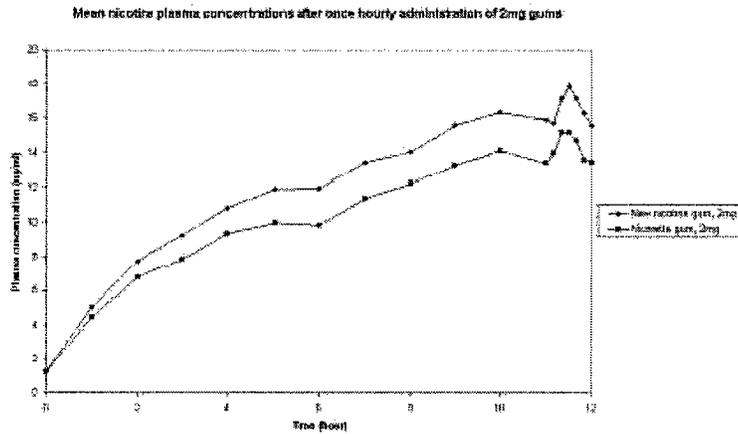
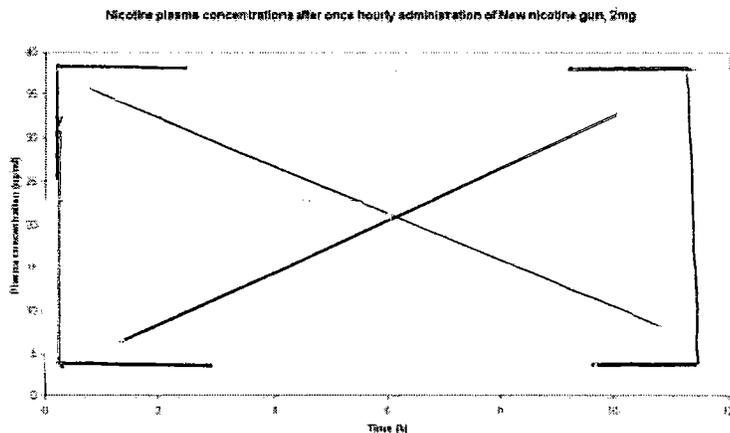
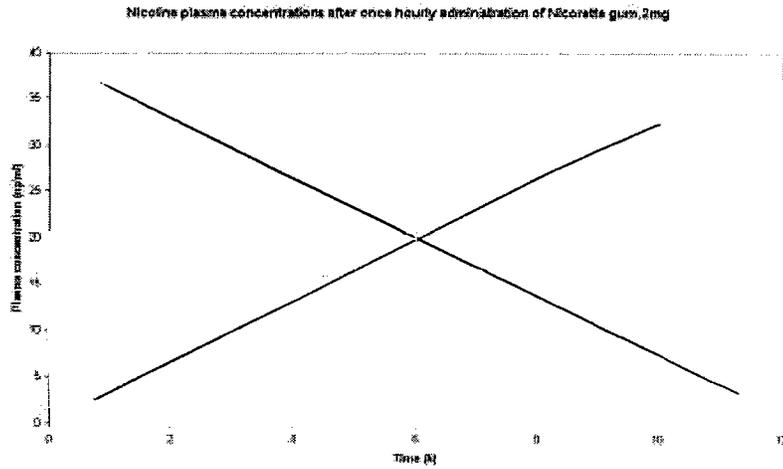


Figure 5. Individual nicotine plasma concentration-time curves (New nicotine gum 2 mg)



**Figure 6. Individual nicotine plasma concentration-time curves
(Nicorette® gum 2 mg)**



Pharmacokinetic parameters (mean \pm SD, median, min - max) . 4 mg gum

Formulation	Dose (mg)	C _{max} (ng/ml)	t _{max} (h)	AUC _{0-t} (h*ng/ml)	AUC _{0-∞} (h*ng/ml)	t _{1/2} (h)
New nicotine gum (n=30)	3.05 \pm 0.38	9.8 \pm 2.7	0.67 \pm 0.27	26.1 \pm 8.1	31.7 \pm 10.0	2.77 \pm 0.83
	3.13	9.2	0.50	24.8	29.4	2.90
	(1.90-3.74)	(5.9 - 17.7)	(0.33 - 1.25)	(11.8 - 48.4)	(15.8 - 59.8)	(1.33 - 4.18)
Nicorette gum (n=31)	2.87 \pm 0.30	8.4 \pm 2.5	0.64 \pm 0.23	22.7 \pm 8.8	28.7 \pm 11.1	2.85 \pm 0.89
	2.87	7.9	0.50	22.4	27.0	2.88
	(2.20-3.39)	(4.9 - 17.7)	(0.33 - 1.00)	(10.2 - 54.0)	(12.7 - 70.6)	(1.34 - 4.95)

Figure 1. Mean nicotine plasma concentrations after single dose administration of 4 mg gum

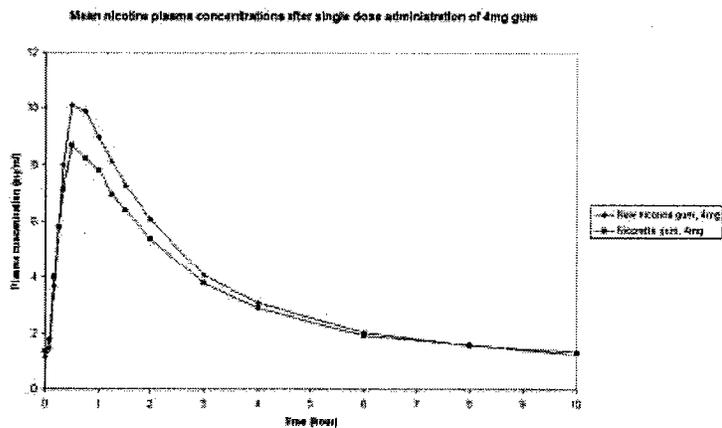


Figure 2. Individual nicotine plasma concentration-time curves (New nicotine gum 4 mg)

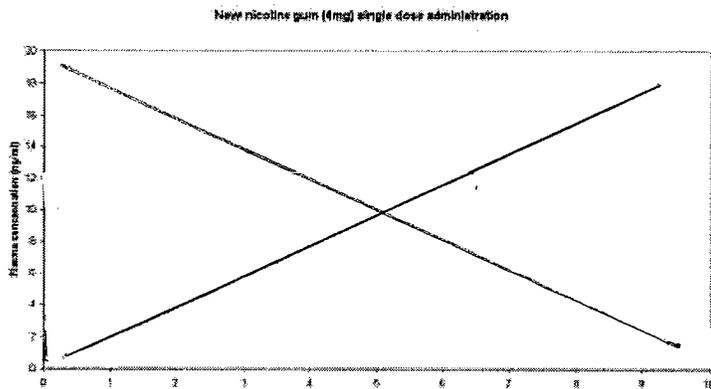


Figure 3. Individual nicotine plasma concentration-time curves (Nicorette gum 4 mg)

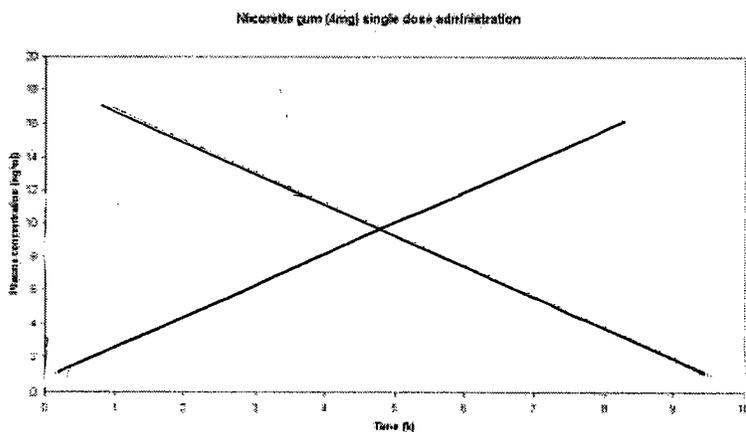


Table 4. Amount of nicotine (mg) released during chewing

Treatment	Dose #	Mean	SD	Median	Range
2 mg New nicotine gum	1	1.47	0.18	1.51	_____
2 mg New nicotine gum	12	1.48	0.18	1.50	_____
2 mg Nicorette [®] gum	1	1.30	0.18	1.33	_____
2 mg Nicorette [®] gum	12	1.33	0.17	1.35	_____
4 mg New nicotine gum	1	3.05	0.38	3.13	_____
4 mg Nicorette [®] gum	1	2.87	0.30	2.87	_____

Table 5. Geometric mean and 90% confidence intervals for ratio New nicotine gum/Nicorette[®] gum

Parameter	Treatment	
	4 mg	2 mg
C_{max}	1.20 (1.12 – 1.28)	1.17 (1.12 – 1.22)
AUC_t	1.21 (1.13 – 1.29)	
AUC_{∞}	1.16 (1.10 – 1.23)	
AUC_{11-12h}		1.16 (1.11 – 1.22)

Table 6. Geometric mean and 90% confidence intervals for ratio New nicotine gum/Nicorette[®] gum after correction for dose

Parameter (corrected for dose)	Treatment	
	4 mg	2 mg
C_{max}	1.13 (1.06 – 1.20)	1.05 (1.01 – 1.10)
AUC_t	1.13 (1.07 – 1.21)	
AUC_{∞}	1.09 (1.04 – 1.15)	
AUC_{11-12h}		1.05 (1.01 – 1.10)

Study # NICSOS-9132-005

Study Title: *Bioequivalence Between Two New Nicotine Gums (2 and 4 mg) and Nicorette® Gum (2 and 4 mg) In an Open, Randomized, Crossover, Phase I Study in Healthy Smoking Volunteers*

Objectives: This study was designed to assess the bioequivalence between the original flavor 2 mg gum and the new mint flavor 2 mg variant, under multiple dose conditions. The study also compares the 4 mg original flavor gum and the 4 mg new mint flavor variant following a single dose..

Study Design: Open-label, single dose (4 mg) and multiple-dose (2 mg), 2x2-way, randomized, cross-over study in healthy adult smokers.

Treatments:

Treatment	Drug	Dose	Regimen
A	New nicotine gum	4 mg	single-dose
B	Nicorette [®] nicotine gum	4 mg	single-dose
C	New nicotine gum	12x2 mg	multiple-dose
D	Nicorette [®] nicotine gum	12x2 mg	multiple-dose

Procedures

A total of 32 healthy smokers (15 male, 17 female) were enrolled in the study. Five subjects withdrew before completion of study. In the single dose treatment six subjects were excluded from the efficacy analysis due to nicotine baseline plasma concentrations >5 ng/ml. In the multiple dose treatment five subjects were excluded from the efficacy analysis due to nicotine baseline plasma.

Twelve repeated doses (administered 1 hour apart) of either new mint or original flavor were administered for the 2 mg gum and one dose of either new mint or original flavor for the 4 mg gum. Upon completion of each phase the subjects were washed out for a week before being crossed over to the other treatment.

Blood sampling for determination of nicotine were drawn pre-dose and at 5, 10, 15, 20, 30, 45 minutes, 1, 1.25 (1 hour 15 minutes), 1.5, 2, 3, 4, 6, 8 and 10 hours after the administration of treatments A and B. The sampling times after treatments C and D were before each dose and at 10, 20, 30, 40, 50 minutes and 1 hour after the last administration. The exact time points for sampling were recorded. Time deviations of 1 minute or more from the planned sampling time were recorded.

The blood samples (5 ml) were collected in heparinized tubes. The plasma was then separated by centrifugation at 1000g for 10 minutes at +4°C. The plasma was then transported, in frozen condition (-20°) to Analytical R&D, Pharmacia AB, Consumer Healthcare, Helsingborg, Sweden., where they were analyzed for nicotine and cotinine (the primary metabolite of nicotine).

Results

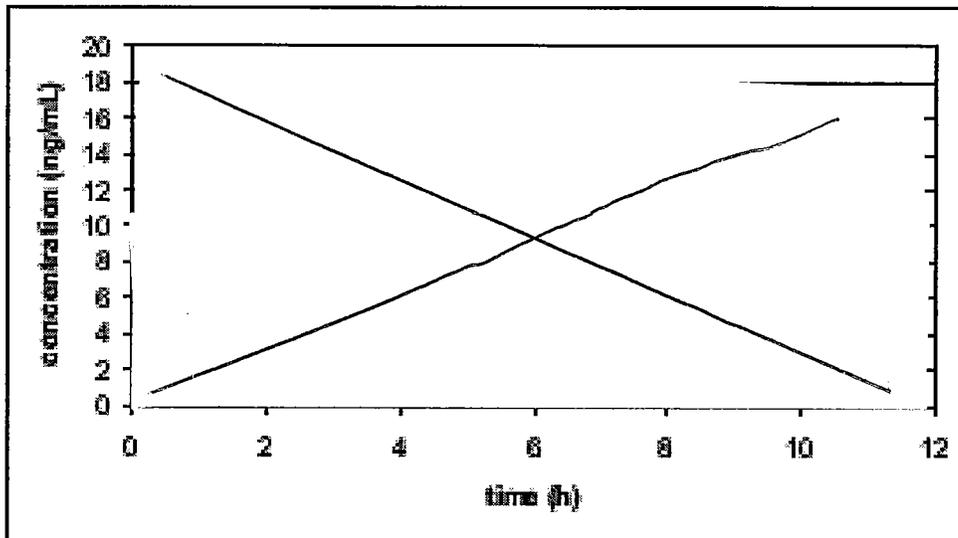
Pharmacokinetic parameters (mean \pm SD, median, min - max) , 4 mg gum

Formulation	Dose ¹ (mg)	C _{max} (ng/ml)	t _{max} (h)	AUC _t (h*ng/ml)	AUC _∞ (h*ng/ml)	t _{1/2} (h)
New nicotine coated gum (n=24)	3.01 \pm 0.36 3.02 (2.01-3.66)	9.6 \pm 3.0 9.7 (4.9 -15.9)	0.78 \pm 0.29 0.75 (0.3 - 1.5)	31.0 \pm 11.0 30.0 (12.8 - 49.4)	31.6 \pm 9.8 31.0 (16.4 - 47.1)	2.53 \pm 0.72 2.6 (1.2 - 4.2)
Nicorette gum (n=24)	2.85 \pm 0.31 2.87 (2.11-3.38)	8.4 \pm 2.4 8.1 (5.4 - 16.2)	0.66 \pm 0.21 0.75 (0.3 - 1.00)	28.6 \pm 9.9 28.1 (11.2 - 54.1)	29.1 \pm 8.5 28.0 (12.7 - 50.8)	2.84 \pm 1.20 2.76 (1.2 - 6.1)

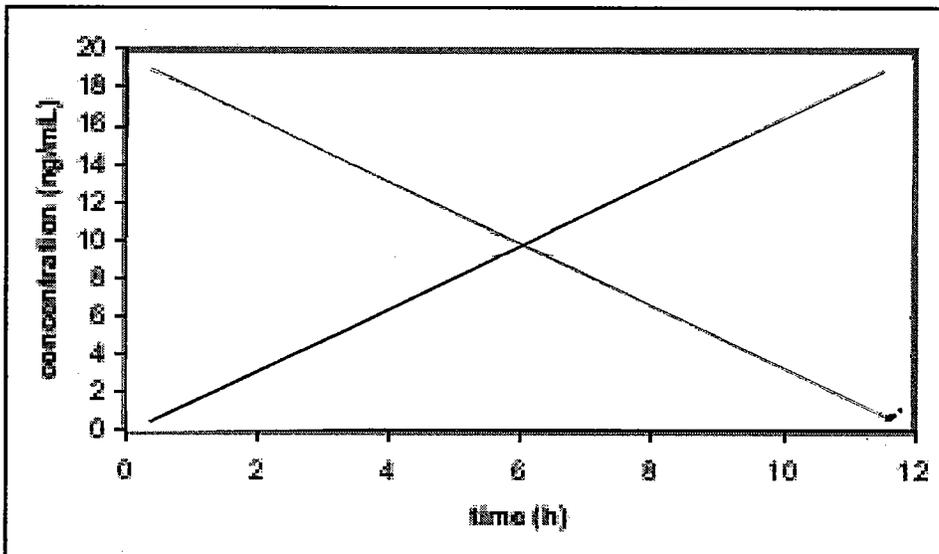
¹ n=30

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**Figure 2. Individual Nicotine Plasma Concentration-time Curves
(New Nicotine Gum 4 mg)**



**Figure 3. Individual Nicotine Plasma Concentration-time Curves
(Nicorette[®] Gum 4 mg)**

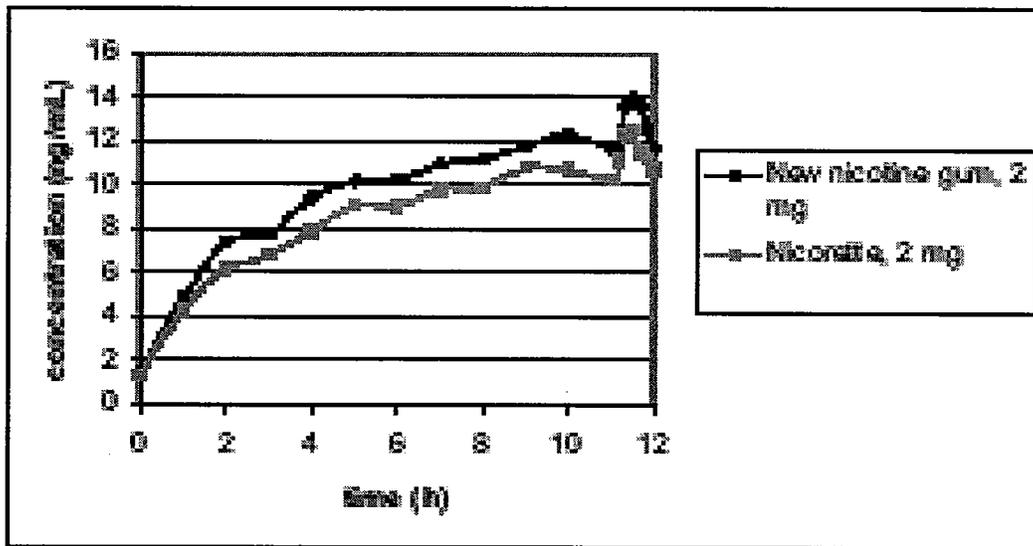


Pharmacokinetic parameters (mean \pm SD, median, min - max) . 2 mg gum

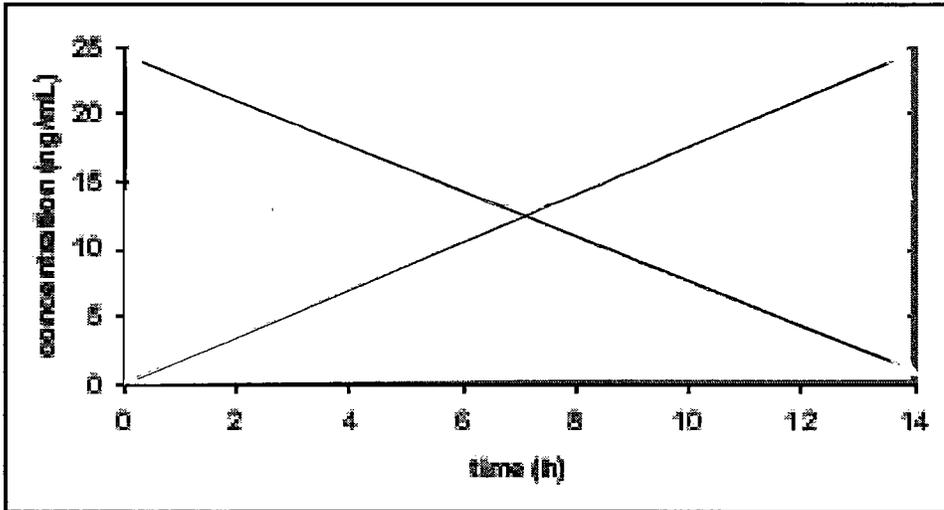
Formulation	Dose ¹ (mg)	C _{max} , 11-12h (ng/ml)	t _{max} (h) ²	AUC _{11-12h} (h*ng/ml) ¹	Peak/ trough ² (%)	Swing ² (%)
New nicotine coated gum (n=22)	1.40 \pm	14.3 \pm 3.6	0.55 \pm 0.16	12.9 \pm 3.4	23 \pm 9	27 \pm 12
	0.23	14.2	0.50	12.9	23	26
	1.40	(8.1-21.9)	(0.3 - 0.8)	(6.9 - 20.4)	(6 - 42)	(6 - 57)
	(0.82- 1.72)					
Nicorette gum (n= 22)	1.26 \pm	12.6 \pm 3.1	0.45 \pm 0.11	11.4 \pm 2.9	20 \pm 8	23 \pm 10
	0.21	12.0	0.50	11.2	18	20
	1.25	(6.2 - 18.3)	(0.2 - 0.7)	(5.2 - 17.1)	(9 - 38)	(9 - 48)
	(0.69- 1.63)					

¹n=27 ²last dosing interval

Figure 4. Mean Nicotine Plasma Concentrations after Once Hourly Administration of 2 mg Gums



**Figure 5. Individual Nicotine Plasma Concentration-time Curves
(New Nicotine Gum 2 mg)**



**Figure 6. Individual Nicotine Plasma Concentration-time Curves
(Nicorette[®] Gum 2 mg)**

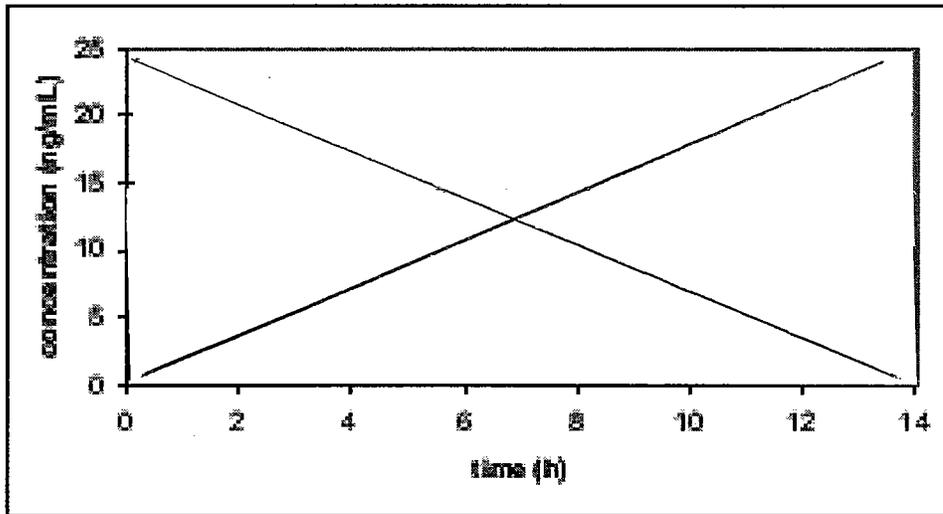


Table 5. Amount of Nicotine (mg) Released during Chewing

Treatment	Dose #	Mean/gum	SD	Median	Min-Max
2 mg New nicotine gum (n=29)	12	1.29	0.25	1.40	↘
2 mg Nicorette® gum (n=28)	12	1.25	0.20	1.25	
4 mg New nicotine gum (n=30)	1	3.01	0.35	3.02	
4 mg Nicorette® gum (n=32)	1	2.85	0.30	2.87	

Table 6. Geometric Mean and 90% Confidence Intervals for Ratio New Nicotine Gum/ Nicorette® Gum

Parameter	Treatment	
	4 mg	2mg
$C_{total}/C_{total, 11-12h}$	1.1345 (1.0295 – 1.2503)	1.1363 (1.0720 – 1.2046)
AUC _{0-12h}	1.0728 (0.9634 – 1.1947)	
AUC _{0-∞}	1.0771 (0.9662 – 1.1763)	
AUC _{11-12h}		1.1276 (1.0672 – 1.1914)

Table 7. Geometric Mean and 90% Confidence Intervals for Ratio New Nicotine Gum/ Nicorette® Gum after Correction for Content of Nicotine in the Gums

Parameter (corrected for added amount of nicotine)	Treatment	
	4 mg	2mg
$C_{total}/C_{total, 11-12h}$	1.1617 (1.0542 – 1.2801)	1.1363 (1.0720 – 1.2046)
AUC _{0-12h}	1.0984 (0.9863 – 1.2332)	
AUC _{0-∞}	1.1027 (1.0095 – 1.2044)	
AUC _{11-12h}		1.1276 (1.0672 – 1.1914)

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/s/

Dennis Bashaw
4/1/04 08:10:22 PM
BIOPHARMACEUTICS

Arzu Selen
4/1/04 08:25:05 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-066 / S-016

CHEMISTRY REVIEW(S)

Chemistry Review #1	1. Division HFD-560	2. NDA & Suppl. No. 18-612/SCF-034, 20-066/SCF-016
3. Name and Address of Applicant GlaxoSmithKline Attention: Zinatara A. Manji, Associate, Regulatory Affairs 1500 Littleton Road, Parsippany, NJ 07054-3884		4. Date of Submission Stamp PDUFA 11/26/03 12/2/03 4/2/04
5. Name of Drug: Nicorette gum	6. Nonproprietary Name: Nicotine polocrilex	
7. Supplement, PAS Provides for: A new mint flavored Nicorette uncoated gum.		8. Amendment(s) 2/5/04, 3/1/04 & 3/29/04
9. Pharmacological Category Smoking cessation aid	10. How Dispensed, OTC	11. Related IND/NDA/DMF DMF 3835
12. Dosage Form: Gums	13. Potency(ies): 2 mg (18-612) 4 mg (20-066)	
14. Route of Administration: Oral, buccal		
15. Comments: GlaxoSmithKline (GSK) requested to add a new mint flavored Nicorette uncoated gum. The active ingredient, Nicotine polacrilex, is a resin complex (polacrilex) containing _____, the same drug substance used in currently marketed Nicorette® gum formulations (Original, Mint and Orange flavors). The drug products, Nicorette® _____ mint Uncoated 2 mg and 4mg gums are manufactured by Pharmacia at their facility in Cork, Ireland, which is a currently approved drug product manufacturing facility. The 2 mg and 4 mg formulations, other than the flavoring, are similar to the currently approved Nicorette® gum formulations (Original, Mint and Orange flavors). Method of manufacture and quality control of the drug product were referenced to Pharmacia's DMF #3835. Tests and acceptance criteria for drug product release and stability are provided. Satisfactory 18 months stability data with drug product stored in blister packaging at room temperature (25°C/60% RH) were submitted. New stability protocols that contained revised impurity limits per ICH 3B were proposed in the amendments of 3/1/04. The sponsor's request for a 24 month expiration date is acceptable. The currently marketed Nicorette® gum formulations (Original, Mint and Orange flavors) carried 36 months expiration dates.		
16. Conclusions and Recommendations: Recommend Approval.		
17. Name of the review chemist		Date
Bart Ho, Chemist		March 19, 2004

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CHEMISTRY REVIEW #1

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/s/

Bartholomew Ho
3/30/04 11:38:40 AM
CHEMIST

John Smith
3/30/04 12:21:26 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-066 / S-016

ADMINISTRATIVE DOCUMENTS



FDA Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville, MD 20857

CONSULTATION

Date: April 2, 2004

To: Laura Shay
Project Manager, DOTCDP (HFD-560)

Through: Bob Rappaport, M.D.
Division Director, DACCADP

From: R. Daniel Mellon, Ph.D.
Supervisory Pharmacologist, DACCADP

Subject: — mint uncoated Nicorette® gum N18-612S/0-34 and N20-066/S-016: Proposal to revise finished product specifications based on additional stability data for a new Mint flavored Nicorette® uncoated gum (2 and 4 mg).

Date of Submission: December 8, 2003

Date Response Requested (Priority): April 2, 2004 (Due April 2, 2004)

Background: GlaxoSmithKline (GSK) is developing a new flavor of Nicorette® gum that is softer and sweeter, in order to increase compliance and reach more of the smoking population who either will not or cannot use the currently marketed gum products due to either real or perceived dissatisfaction with the current tastes and flavors. The new formulation is called Nicorette® — mint Uncoated gum and was shown to be bioequivalent with the current marketed products.

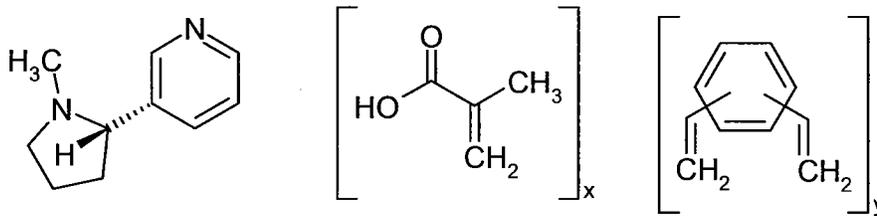
Nicorette® gum comes in 2 mg and 4 mg strengths. According to the labeled directions for use, the maximum number of pieces you should chew a day is 24. Therefore, the

maximum daily nicotine exposure for the 2 mg and 4 mg gum would be 48 and 96 mg nicotine, respectively. Based upon this total daily intake (TDI), the qualification threshold for degradation products/impurities in the drug product would be set at 0.5% or 200 µg TDI, which ever is lower (ICHQ3BR). For the 2 mg gum product, 0.5% of 48 mg would be 240 µg TDI. For the 4 mg gum product, 0.5% of 96 mg would be 480 µg TDI. As such the ICH Q3BR specification for both drug products is 200 µg TDI.

GSK electronically submitted 2 chemistry supplements to their Nicorette® Gum NDAs as follows:

SCF034 Nicorette® 2 mg uncoated gum (NDA 18-612)
 SCF016 Nicorette® 4 mg uncoated gum (NDA 20-066)

In addition, on March 1, 2004 and then again on March 29, 2004, GSK submitted amendments to these supplements (BC) that contains "finished product specifications"....these amendments are also in the EDR. The DMF for the drug substance, nicotine polacrilex (figure below) is held by Pharmacia and Upjohn Company, who authorized FDA to review DMF — in support of the supplement.



Pharmacia and Upjohn Company consider the stability of the drug substance to be proprietary and thus that information is only in DMF —. The drug product is manufactured by Pharmacia (DMF 3835) in the Helsingborg, Sweden facility. This site has already been approved for Nicorette® Original, Nicorette® Mint and Nicorette® Orange (2 and 4 mg).

The components of the — Mint Formulation are listed in the sponsor's table below:

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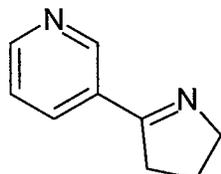
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4/2/04 CONSULT

Myosmine is a minor alkaloid in tobacco. Until recently, human exposure to myosmine was thought to only occur via tobacco. However, myosmine can be detected in a wide variety of foods, including nuts and nut products, corn, rice, wheat flour, millet, potato, milk, cocoa, popcorn, tomato, carrot, pineapple, kiwi and apples. The levels of exposure to myosmine via common food staples could lead to an average dietary myosmine uptake of 475 µg/year (Tyroller et al., 2002).



Myosmine

Acute Toxicology: From the RTECs database

LD₅₀/LC₅₀ - LETHAL DOSE/CONC 50% KILL

Rat

LD₅₀ - ROUTE: Intraperitoneal; DOSE: 190 mg/kg

TOXIC EFFECTS:

Behavioral - Convulsions or effect on seizure threshold

LD₅₀ - ROUTE: Oral; DOSE: 1875 mg/kg

TOXIC EFFECTS:

Behavioral - Convulsions or effect on seizure threshold

Genetic Toxicology: Myosmine induced repairable DNA damage in a test with *Escherichia coli* pol A+/pol A- but was negative in the Ames test (Riebe et al., 1982). Myosmine did not enhance the frequency of sister chromatid exchanges in CHO cells (Riebe and Westphal, 1983). More recently myosmine was reported to test positive in the alkaline single cell microgel electrophoresis assay (Comet) to detect DNA single strand breaks (Kleinsasser et al., 2003).

Evidence exists that myosmine is metabolized to normicotine. Normicotine can be nitrosated under acidic conditions and a nitrate source, to nitrosonornicotine (NNN), a strong animal carcinogen and suspected human carcinogen (Wilp et al., 2002).

Recommendation:

At this time, the final specifications for — mint uncoated Nicorette® 2 mg and 4 mg gum products are acceptable from a pharmacology and toxicology perspective. However,

the sponsor should _____ to
positive genetic toxicology reports in the literature and the potential conversion to nitrosocompounds.

Reference List

Kleinsasser NH, Wallner BC, Harreus UA, Zwickenpflug W, and Richter E (2003) Genotoxic effects of myosmine in human lymphocytes and upper aerodigestive tract epithelial cells. *Toxicology* **192**:171-177.

Riebe M and Westphal K (1983) Studies on the induction of sister-chromatid exchanges in Chinese hamster ovary cells by various tobacco alkaloids. *Mutat.Res.* **124**:281-286.

Riebe M, Westphal K, and Fortnagel P (1982) Mutagenicity testing, in bacterial test systems, of some constituents of tobacco. *Mutat.Res.* **101**:39-43.

Tyroller S, Zwickenpflug W, and Richter E (2002) New sources of dietary myosmine uptake from cereals, fruits, vegetables, and milk. *J.Agric.Food Chem.* **50**:4909-4915.

Wilp J, Zwickenpflug W, and Richter E (2002) Nitrosation of dietary myosmine as risk factor of human cancer. *Food Chem.Toxicol.* **40**:1223-1228.

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/s/

R. Daniel Mellon
4/2/04 01:03:25 PM
PHARMACOLOGIST

Bob Rappaport
4/2/04 05:38:54 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-066 / S-016

CORRESPONDENCE



GlaxoSmithKline

April 6, 2004

Charles Ganley, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Division of Over-the-Counter Drug Products, HFD-560
Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ
07054-3884

Tel. 973 889 2100
Fax. 973 889 2390
www.gsk.com

**Re: Supplemental New Drug Application NDA 20-066/S-016
Nicorette® (nicotine polacrilex) 4 mg Gum
Amendment #4: Complete Response to Approvable Letter (4/02/2004)**

Dear Dr. Ganley:

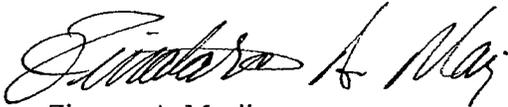
Reference is made to NDA 20-066/S-016 dated November 26, 2003 for a new mint flavored Nicorette® (nicotine polacrilex) 4 mg uncoated gum. Reference is also made to an Approvable Letter sent by the Agency on April 2, 2004. This Amendment addresses the deficiencies noted in the referenced approvable letter.

An exact copy of the information provided herein is also contained in a submission of a Supplemental New Drug Application for Nicorette® 2 mg gum (NDA 18-612) sent under separate cover.

This submission has been organized into a folder-based structure in compliance with the guidance for providing regulatory submissions in electronic format (IT3 January 1999). The total size of the submission is approximately 1 MB, and is contained on one CDROM. It has been confirmed as virus free using Norton Antivirus software (version 7.61.930, scan engine 4.1.0.15, updated 1/21/2004) from Symantec.

Please contact the undersigned by phone at (973)-889-2322 or by fax at (973)-889-2501 with any questions relating to this Supplemental New Drug Application.

Sincerely,



Zinatara A. Manji
Associate, Regulatory Affairs

CC: Laura Shay
Regulatory Project Manager

March 12, 2004



GlaxoSmithKline

Charles Ganley, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Division of Over-the-Counter Drug Products, HFD-560
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**Re: Supplemental New Drug Application NDA 20-066/S-016
Nicorette® (nicotine polacrilex) 4 mg Gum
Amendment #3
Revised Labeling – User's Guide**

Dear Dr. Ganley:

Reference is made to NDA 20-066/S-016 dated November 26, 2003 for a new mint flavored Nicorette® (nicotine polacrilex) 4 mg uncoated gum. Reference is also made to NDA 20-066/S-017 submitted December 23, 2003 to propose modifications to current labeling for Nicorette® 2 mg and 4 mg (Original, Mint and Orange) gum and the subsequent Amendment #1, submitted March 12, 2004. In accordance with the Agency's response to NDA 20-066/S-017, sent on February 24, 2004, the User's Guide was revised and submitted in Amendment #1. In order to maintain consistency between these two supplements, enclosed please find an amended User's Guide. The Agency's changes to carton labeling, in the above referenced letter (S-017), will be reflected in the final printed labeling for this supplement (S-016).

An exact copy of the information provided herein is also contained in a submission of a Supplemental New Drug Application for Nicorette® 2 mg gum (NDA 18-612) sent under separate cover.

This submission has been organized into a folder-based structure in compliance with the guidance for providing regulatory submissions in electronic format (IT3 January 1999). The total size of the submission is approximately 1 MB, and is contained on one CDROM. It has been confirmed as virus free using Norton Antivirus software (version 7.61.930, scan engine 4.1.0.15, updated 3/18/2004) from Symantec.

Please contact the undersigned by phone at (973)-889-2322 or by fax at (973)-889-2501 with any questions relating to this Supplemental New Drug Application.

Sincerely,



Zinatara A. Manji
Associate, Regulatory Affairs

CC: Laura Shay
Regulatory Project Manager

March 1, 2004



GlaxoSmithKline

Charles Ganley, M.D.
Food and Drug Administration
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Office of Drug Evaluation V
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**Re: Supplemental New Drug Application NDA 20-066/S-016
Nicorette® (nicotine polacrilex) 4 mg Gum
Amendment #2
CMC: Revised Finished Product Specifications**

Dear Dr. Ganley:

Reference is made to NDA 20-066/S-016 dated November 26, 2003 for a new mint flavored Nicorette® (nicotine polacrilex) 4 mg uncoated gum. Reference is also made to Item 4: Chemistry, Manufacturing and Controls in this supplemental application. This amendment reflects data generated from additional stability information. Stability data on nicotine related impurities and degradation products indicate that _____

_____ For convenience in review, we have republished the Methods Validation Package to incorporate these changes.

This submission has been organized into a folder-based structure in compliance with the guidance for providing regulatory submissions in electronic format (IT3 January 1999). The total size of the submission is approximately 17 MB, and is contained on one CDROM. It has been confirmed as virus free using Norton Antivirus software (version 7.61.930, scan engine 4.1.0.15, updated 1/21/2004) from Symantec.

Please contact the undersigned by phone at (973)-889-2322 or by fax at (973)-889-2501 with any questions relating to this Supplemental New Drug Application.

Sincerely,



Zinatara A. Manji
Associate, Regulatory Affairs

CC: Laura Shay
Regulatory Project Manager



NDA 20-066/S-016

PRIOR APPROVAL SUPPLEMENT

GlaxoSmithKline Consumer Healthcare
Attention: Zinatara A. Manji
Associate, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Ms. Manji:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Nicorette® 4mg (nicotine polacrilex) gum

NDA Number: 18-612

Supplement number: 034

**APPEARS THIS WAY
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Date of supplement: November 26, 2003

Date of receipt: December 2, 2003

This supplemental application proposes a new mint flavored uncoated gum.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 31, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the goal date will be April 2, 2004.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
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If you have any questions, call Laura Shay, Regulatory Project Manager, at (301) 827-2274.

Sincerely yours,

{See appended electronic signature page}

David Hilfiker

Chief, Project Management Staff

Division of Over the Counter Drug Products

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David Hilfiker
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