CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 021330/S-002

Name: Commit® (nicotine polacrilex) Lozenge

Sponsor: GlaxoSmithKline Consumer Healthcare

Approval Date: February 13, 2004

This supplemental new drug application provided for a new spearmint flavored Commit® Spearmint (nicotine polacrilex) Lozenge.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021330/S-002

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Approvable Letter	
Labeling	**X**
Division Director's Memo	
Labeling Review(s)	**X**
Medical Review(s)	
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology / Toxicology Review(s)	**X**
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology & Biopharmaceutics Review(s)	**X**
Other Review(s)	
Administrative and Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021330/S-002

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-330/S-002

GlaxoSmithKline Consumer Healthcare
Attention: David Schifkovitz
Director, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Mr. Schifkovitz:

Please refer to your supplemental new drug application dated March 12, 2003, received March 14, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Commit® (nicotine polacrilex) Lozenge.

We acknowledge receipt of your submission dated October 15, 2003.

Your submission of October 15, 2003, constituted a complete response to our July 14, 2003, Approvable letter.

This supplemental new drug application provided for a new spearmint flavored Commit® Spearmint (nicotine polacrilex) Lozenge.

We completed our review of this supplemental new drug application, as amended. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on March 12, 2003.

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 the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Charles Ganley

2/13/04 10:19:29 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021330/S-002

LABELING

Commit Lozenge
72ct. 4mg
Front Panel

Drug Facts

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

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

Use

- reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings

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

Do not use

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

Ask a doctor before use if you have

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

Ask a doctor or pharmacist before use if you are

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

Stop use and ask a doctor if

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

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

Directions

- **if you are under 18 years of age, ask a doctor before use**
- before using this product, read the enclosed User's Guide for complete directions and other important information ▶

Drug Facts (continued)

Directions

- stop smoking completely when you begin using the lozenge
- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2mg nicotine lozenge
- **if you smoke your first cigarette within 30 minutes of waking up,** use 4mg nicotine lozenge according to the following 12 week schedule:

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

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

Other information

- Phenylketonurics: Contains Phenylalanine 3.4 mg per lozenge
- store at 20 - 25°C (68 - 77°F)
- protect from light

Inactive ingredients

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

Questions or comments?

call weekdays **1-888-569-1743** (10:00am - 4:30pm EST)

Commit Lozenge

72ct. 4mg

Back / Top Panel

From the marketers of
Nicorette®
Commit™

TO INCREASE YOUR SUCCESS IN QUITTING:

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

To remove the lozenge, tear off single unit. | Peel off backing starting at corner with loose edge. | Push lozenge through foil.

*The American Cancer Society supports the use of stop smoking aids and counseling as effective tools when quitting smoking but does not endorse any specific product. GlaxoSmithKline pays a fee to the American Cancer Society for the use of its logo.

Distributed By:
GlaxoSmithKline Consumer Healthcare, L.P.
Pittsburgh, PA 15230, Made in the U.S.A.

00000XX

From the marketers of
Nicorette®
Commit™

- 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

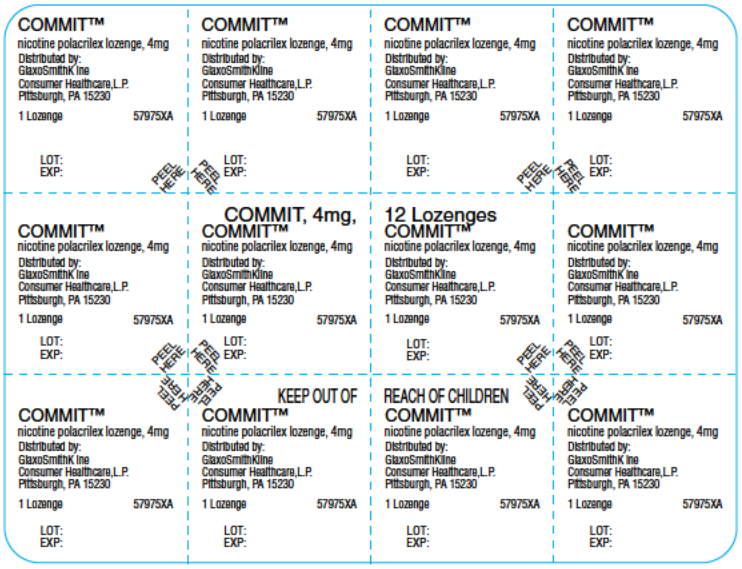
Blister packaged for your protection.

Do not use if individual seals are open or torn.

Internal theft surveillance system

0 0000-0000-00 0

Commit Lozenge
72ct. 4mg
Side Panels



GlaxoSmithKline	PACKAGING SPECIFICATION	Date: 6.24.02

(b) (4)

BRAND: Commit	UPC/SKU NO.: n/a
PROD. CATEGORY: Smoking Cessation	E.V. NO.: n/a
DESCRIPTION: Blister	DIMENSIONS: 80mm x 105mm
COMPONENT: Lozenge	DIE NO.: NPL0002PM
VOLUME CONTENTS/SIZE: 72ct 4mg	MANUFACTURING SITE: Aiken
FORM NO.: 57975XA	PRINTER: (b) (4)
COUNTRY: USA	PREPRESS
PMS COLORS: Black	REPLACES FORM NO.: New
KEYWORDS:	PRF NO.: 211-02
Artist: (b) (6)	Revision 1: (b) (6) 5.26.02-refit copy to die
Computer Software: Adobe Illustrator 8.0	Revision 2: 5.26.02-added "peel here"

PS03

GlaxoSmithKline	Regulatory Artwork Approval
SIGNATURE:	DATE:
COMMENTS:	

REG02

PRINTER
PLEASE NOTE YOUR RESPONSIBILITIES:

- Use existing die. Die line for art position only.
- Verify all bar codes meet ANSI standards.
- Fonts included solely for this artwork and recreating this specific file. GlaxoSmithKline requires that all fonts be destroyed upon completion of this project.
- These files are not trapped.

PMS COLOR CHIPS:

Black

Commit Lozenge
72ct. 2mg
Front Panel

Drug Facts

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

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

Use

- reduces withdrawal symptoms, including nicotine craving, associated with quitting smoking

Warnings

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

Do not use

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

Ask a doctor before use if you have

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

Ask a doctor or pharmacist before use if you are

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

Stop use and ask a doctor if

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

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

Directions

- **if you are under 18 years of age, ask a doctor before use**
- before using this product, read the enclosed User's Guide for complete directions and other important information ▶

Drug Facts (continued)

Directions

- stop smoking completely when you begin using the lozenge
- **if you smoke your first cigarette within 30 minutes of waking up,** use 4mg nicotine lozenge
- **if you smoke your first cigarette more than 30 minutes after waking up,** use 2mg nicotine lozenge according to the following 12 week schedule:

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

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

Other information

- Phenylketonurics: Contains Phenylalanine 3.4 mg per lozenge
- store at 20 - 25°C (68 - 77°F)
- protect from light

Inactive ingredients

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

Questions or comments?

call weekdays **1-888-569-1743** (10:00am - 4:30pm EST)

Commit Lozenge

72ct. 2mg

Back / Top Panel

From the marketers of
Nicorette®
Commit™

TO INCREASE YOUR SUCCESS IN QUITTING:

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

To remove the lozenge, tear off single unit. | Peel off backing starting at corner with loose edge. | Push lozenge through foil.

*The American Cancer Society supports the use of stop smoking aids and counseling as effective tools when quitting smoking but does not endorse any specific product. GlaxoSmithKline pays a fee to the American Cancer Society for the use of its logo.

Distributed By:
GlaxoSmithKline Consumer Healthcare, L.P.
Pittsburgh, PA 15230, Made in the U.S.A.

00000XX

From the marketers of
Nicorette®
Commit™

- 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

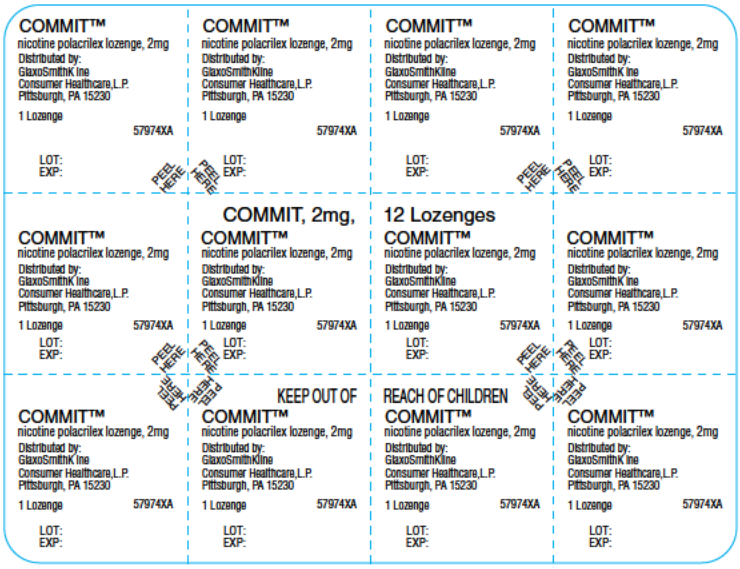
Blister packaged for your protection.

Do not use if individual seals are open or torn.

Internal theft surveillance system

0 0000-0000-00 0

Commit Lozenge
72ct. 2mg
Side Panels



GlaxoSmithKline	PACKAGING SPECIFICATION	Date: 6.24.02
		(b) (4)
BRAND: Commit		UPC/SKU NO.: n/a
PROD. CATEGORY: Smoking Cessation		E.V. NO.: n/a
DESCRIPTION: Blister		DIMENSIONS: 80mm x 105mm
COMPONENT: Lozenge		DIE NO.: NPL0002PM
VOLUME CONTENTS/SIZE: 72ct 2mg		MANUFACTURING SITE: Aiken
FORM NO.: 57974XA		PRINTER: (b) (4)
COUNTRY: USA		PREPRESS
PMS COLORS: Black		REPLACES FORM NO.: New
KEYWORDS:		PRF NO.: 211-02
Artist: (b) (6)		Revision 1: (b) (6) 6.26.02-refit copy to die
Computer Software: Adobe Illustrator 8.0		Revision 2: 6.26.02-added "peel here" copy

PS03

GlaxoSmithKline	Regulatory Artwork Approval
SIGNATURE:	DATE:
COMMENTS:	

REG02

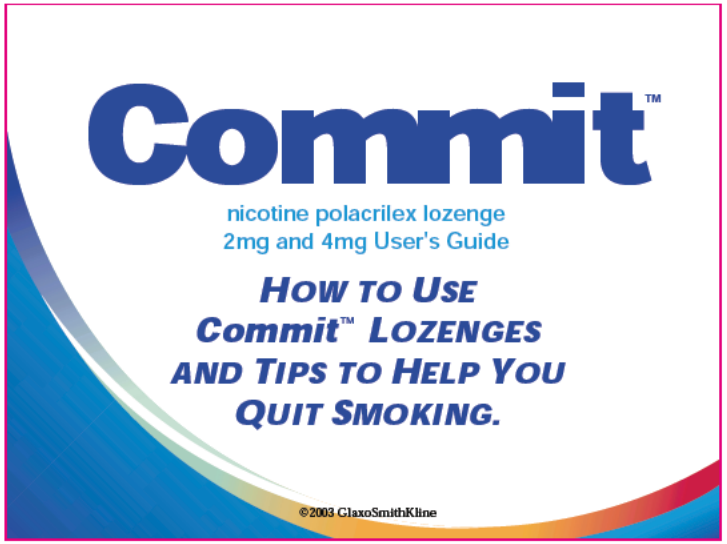
PRINTER

PLEASE NOTE YOUR RESPONSIBILITIES:

- Use existing die. Die line for art position only.
- Verify all bar codes meet ANSI standards.
- Fonts included solely for this artwork and recreating this specific file. GlaxoSmithKline requires that all fonts be destroyed upon completion of this project.
- These files are not trapped.

PMS COLOR CHIPS:

Black


Commit™
nicotine polacrilex lozenge
2mg and 4mg User's Guide
HOW TO USE
Commit™ LOZENGES
AND TIPS TO HELP YOU
QUIT SMOKING.
©2003 GlaxoSmithKline

- **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.**

PLANNING YOUR SUCCESS

1) The key to accomplishing anything important is commitment. When it comes to quitting smoking, that is especially true. **Commit**™ Lozenges can help if you really want to quit. **Commit**™ Lozenges help reduce withdrawal symptoms including nicotine craving associated with quitting smoking.
2) Your chances of staying off cigarettes are much better if you start with at least 9 **Commit**™ Lozenges daily. For best results, use the lozenges on a regular schedule (as outlined in this User's Guide).
3) Stop smoking completely when you start using **Commit**™ Lozenges. Even a single cigarette is likely to put you right back to square one.
4) This User's Guide outlines a 12-week plan for **Commit**™ Lozenges. Even though you may feel confident about your non-smoking status after a few weeks, it's important to stick with the plan to help you remain smoke free.
5) **Commit**™ Lozenges work best when used together with a support plan. See insert between pages 8 and 9 for instructions on enrollment in the Committed Quitters Personalized Stop Smoking Plan.
6) After the first six weeks, start using fewer **Commit**™ Lozenges, as directed in the instructions, so you can become smoke-and nicotine-free by the end of the 12 week plan.
7) If you have questions about using **Commit**™ Lozenges, call 1-888-569-1743 weekdays (10:00am - 4:30pm EST), or talk to your pharmacist or family doctor.

YES! YOU WANT TO QUIT.

Wonderful. You've made the most important decision of all, to stop smoking. And by choosing **Commit**™ Lozenges to help you, you're starting on the right path. Now remember, using **Commit**™ doesn't just mean taking a

Commit™ Lozenge. It means setting and following a program like the one we suggest in this User's Guide.

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

LET'S FACE IT.

Quitting smoking isn't easy! You or someone you know may have tried unsuccessfully. That's okay. It's hard to stop smoking the first time you try. The important part is to learn from your previous attempts, consider what went wrong and keep trying to quit until you succeed.

Look to this User's Guide for support as you undergo this terrific task. The guide includes important information on how to use **Commit**™ Lozenges and also gives you tips to help you stop smoking. Refer back to it often for advice, answers, and encouragement to help you stay on track.

GET MOTIVATED. STAY MOTIVATED.

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

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

UNDERSTANDING THE DOUBLE-EDGED SWORD.

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

IMPORTANT WARNINGS

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

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

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 ulcers or diabetes.

Ask a doctor or pharmacist before use if you are

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

Stop use and ask a doctor if

- mouth problems occur
- persistent indigestion or severe sore throat occurs
- irregular heartbeat or palpitations occur

Stop use and ask a doctor if (cont.)
- you get symptoms of nicotine overdose such as nausea, vomiting, dizziness, diarrhea, weakness and rapid heartbeat

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

YOU'RE READY TO START.

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

THE PROGRAM

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

Use a **Commit**™ Lozenge every 1 to 2 hours and at least 9 lozenges each day for the first 6 weeks to help prevent unexpected cravings and improve your chances of quitting. **These aren't ordinary lozenges.** Place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20 – 30 minutes). Minimize swallowing. **Do not chew or swallow the lozenge**. You may feel a warm or tingling sensation. Occasionally move the lozenge from one side of your mouth to the other until completely dissolved (about 20 to 30 minutes). **Remember to read the instructions on page 7 before you take your first Commit™ Lozenge.**

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

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

END. At the end of week 12 stop using Commit™ Lozenges to become both cigarette and nicotine-free.

Put the "EX-SMOKER" sticker on your calendar on the date 12 weeks after the day you stopped smoking and started using **Commit**™ Lozenges. You should not use **Commit**™ Lozenges beyond this date.

BE PREPARED.

Since smoking is an addiction, it is hard to quit. Even after you stop, there will be times when you WANT a cigarette, sometimes strongly. (See also section on "Challenges To Watch For"). The best

defense is to be prepared. Plan now for handling tough times so you don't give in. For example: think about situations when you usually get a craving for cigarettes or where you think you might experience strong cravings. Try to avoid these situations where you can (for example, avoid spending time with smokers, or drinking alcohol, if those things tempt you to smoke).

Change your habits. For example, take your coffee break somewhere else. Take a walk. In other words, break the association between your usual habits and cigarettes.

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

To prepare for tough situations, assemble a "survival package"—items that can keep you distracted in case you get a craving. For example, you may include cinnamon gum or hard candy, relaxing music, and things to keep your hands busy like a smooth stone, paper clips, or a rubber ball.

Track your progress as you quit. Keep a journal. Write down how many pieces of **Commit**™ Lozenges you use each day. Note if and when you get a craving. If you slip and have a cigarette, don't give up. Stop smoking again and get back on your program with **Commit**™ Lozenges.

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

Reward yourself. Set aside little gifts to yourself such as a CD or video, which you can earn by overcoming difficult hurdles.

HOW Commit™ LOZENGES WORK.

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

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

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

USING Commit™ LOZENGES PROPERLY.

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

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

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

IMPORTANT: Don't worry or give up if you do not like the taste of the lozenge at first. Commit™ Lozenges are a medication, not a candy. Most people get used to the taste after a day or two. Remember, staying with the plan will help you quit. Stop smoking completely before you start using Commit™ Lozenges.

1) Remove the **Commit**™ Lozenge from the blister. Place the lozenge in your mouth and allow the lozenge to slowly dissolve (about 20 – 30 minutes). Minimize swallowing. **Do not chew or swallow the lozenge**. You may feel a warm or tingling sensation.
2) Occasionally move the lozenge from one side of your mouth to the other side until completely dissolved (about 20-30 minutes).

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

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

Do not use more than 5 lozenges in 6 hours. **Do not use more than 20 lozenges per day**. Stop using the lozenge at the end of 12 weeks (3 months).

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

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

CUTTING BACK ON YOUR Commit™ LOZENGE USAGE.

The whole reason for using **Commit**™ Lozenges is to decrease and slowly eliminate your need for nicotine, while you control cravings. So, as the above schedule indicates, you should gradually reduce the amount of **Commit**™ Lozenges you take per day. Some people find it easier to reduce by substituting ordinary sweets or sugar free candy for some of the **Commit**™ Lozenges they would normally use. As time goes on, you can increase the number of pieces of candy as you further reduce your use of **Commit**™ Lozenges. **Stop using Commit**™ **Lozenge at the end of week 12**. If you still feel the need to use **Commit**™ Lozenge after week 12, talk with your doctor.

MAKE QUITTING EASIER ON YOURSELF.

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

The Day You Quit Smoking:

- Look to your family and friends for support. Let them know what to do or avoid doing to help you quit.
- Throw away ALL cigarettes, ashtrays, matches, lighters. You don't need them. You don't want them and you want to make it difficult to go back.
- Keep yourself occupied. Take a walk. See a movie. See friends. Do anything to keep your mind off cigarettes.
- Calculate all the money you'll save by not buying cigarettes. Probably well over $1,000 a year! $1,000 a year? Think of what you can spend it on!
- Know what situations are going to make you want to smoke. Plan now how you'll avoid them or deal with them so you don't smoke.
- Keep **Commit**™ Lozenges next to your


PLACE THESE STICKERS ON YOUR CALENDAR:
STEP 1
1 lozenge every 1 to 2 hours
STEP 2
1 lozenge every 2 to 4 hours
AT BEGINNING OF WEEK #1 (QUIT DATE)
AT BEGINNING OF WEEK #7
©2003 GlaxoSmithKline
COMMITTED QUITTERS®
Personalized Stop Smoking Plan
brought to you by
Commit™
nicotine polacrilex lozenge
and
GlaxoSmithKline
COMMIT™, COMMITTED QUITTERS®, and associated logo designs and overall trade dress designs are trademarks owned and/or licensed to GlaxoSmithKline or its affiliated companies.
FREE
Personalized Stop Smoking Plan

What is COMMITTED QUITTERS®

- A **FREE**, custom-tailored plan to help you break the psychological addiction to smoking.
- Throughout your quit attempt, you will receive personalized advice on how to cope with situations that make you want to smoke.

TO JOIN COMMITTED QUITTERS®

Personalized Stop Smoking Plan

Enroll online at www.committedquitters.com

or call 1-800-770-0708

and ask for your FREE Personalized Stop Smoking Plan

- Provide your **PERSONAL CODE**, printed on the back of this insert.
- You will be personally interviewed by a plan specialist to understand your specific needs and to design a Stop Smoking Plan just for you.


Read and follow label directions
© 2003 GlaxoSmithKline
PERSONAL CODE
Call Between 7 am and 12 midnight EST
or enroll online 24 hours a day
(ONE PLAN PER CUSTOMER)
COMMITTED QUITTERS®
PLACE THESE STICKERS ON YOUR CALENDAR:
STEP 3
1 lozenge every 4 to 8 hours
EX-SMOKER
AT BEGINNING OF WEEK #10
12 WEEKS AFTER QUIT DATE
©2003 GlaxoSmithKline

bed so you're prepared when you get up. A lot of people get cravings first thing in the morning.

- Make an appointment to see your dentist and get the tobacco stains cleaned off. While you're getting rid of the evidence of cigarettes in the house, do the same for your teeth. Have clothes or drapes that smell of smoking cleaned.
- Now that your house is smoke-free, try to spend most of your time in smoke-free environments.
- If you usually smoked with coffee or alcohol, try to keep away from them for now. Remember you are also trying to break a habit.
- Smoking is a "hands-on" habit. So use something else to occupy your hands: a rubber band or a pen.
- Now's a good time to get active. Find activities to take your mind off cigarettes and relax. Take up jogging, swimming, or walking.
- Don't stress out about gaining weight. Dieting now may weaken your efforts to quit smoking. Eat sensibly and exercise daily; drink large quantities of water and fruit juices; this can help your chances of staying smoke-free.
- Laugh. Watch a sitcom. Read a comic book. It really helps.

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

WHAT YOU CAN EXPECT.

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

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

After a Couple of Weeks. Your confidence and ability to cope with urges to smoke should be getting stronger. But don't be over-confident and think you can smoke just one cigarette. Even now, having even a single puff can lead to a return to smoking cigarettes regularly. Be prepared and remember why you wanted to stop smoking.

Have you noticed that your sense of taste and smell has improved? You are probably coughing less and finding it easier to breathe. You've also probably noticed your withdrawal symptoms are subsiding (though don't worry if they're still there: they last longer for some people). These are all positive signs that your body is getting used to your success at stopping smoking.

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

What If You Do Slip And Smoke?
"What if I relapse?" One cigarette is a slip-up, but it's not the end of the quit

effort. Everybody slips at something. The key is this: forgive yourself and stop at that one cigarette. Don't let this slip ruin your good intentions, keep at your quit attempt. So, throw out your cigarettes and continue with your quit attempt, keeping in mind what went wrong and led to the slip.

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

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

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

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

YOU'VE MADE IT.

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

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

Think of what you're going to do with your newly liberated cigarette money. The places you can now go smoke-free.

Think of the extra time you may have added to your life and what you can do with it. And although you may still experience the occasional temptation, and cigarettes still want you back, think positively. Think forward. And consider yourself a proud non-smoker.

FREQUENTLY ASKED QUESTIONS.

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

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

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

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

cigarettes. Remember, don't use **Commit**™ Lozenges together with nicotine patches or other nicotine containing products.

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

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

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

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

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

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

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

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

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

Automatic slips.
Sometimes you may find yourself preparing to smoke without even realizing it. Watch out for those moments when your hand seems to 'automatically' reach for a cigarette. Watch out for these situations: they can trigger a relapse. You probably know which one (s) are most dangerous for you; plan ahead to deal with the situation effectively. Always remember that you're trying to break a habit, and the most important thing is to do something to combat the urge in these situations.

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

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

59185XB

16

WALLET CARD

My most important reasons to quit smoking are:


2966
WALLET CARD
WHERE TO CALL FOR HELP:
American Lung Association
1-800-586-4872
American Cancer Society
1-800-227-2345
American Heart Association
1-800-242-8721
Quitting Buddy or Friend who has Quit
©2003 GlaxoSmithKline
59185XB

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021330/S-002

LABELING REVIEWS

Labeling Review
Division of OTC Drug Products

NDA #: 21-330	**Sponsor:** GlaxoSmithKline Consumer Healthcare
Drug Product: Nicotine Polacrilex Lozenges, 2 mg and 4 mg	**# of Stock Keeping Units in Submission:** 2
Submission Date: March 12, 2003	**Review Date:** June 10, 2003
Type of Submission: SCF-002	**Reviewer:** Mary S. Robinson, HFD-560

Background
This review is based on GlaxoSmithKline's March 12, 2003 submission of NDA 21-330 for Commit™ 2 mg and 4 mg nicotine polacrilex lozenge. This submission is for a spearmint flavored Commit™ (nicotine polacrilex) Lozenge. Although the original Commit™ (approved October 31, 2002) provided a mild mint flavor, the sponsor states that the new spearmint flavor would better mask the unpleasant taste of this product. The flavor formulation change between this flavor variation and the original flavor lozenge (b) (4) of the lozenge (b) (4). However, all other excipients, manufacturing and packaging processes and configurations between the spearmint lozenge and the original mint flavored lozenge are identical.

Full color printed labeling of the 2 mg and 4 mg Commit™ nicotine polacrilex lozenge for the 72 count cartons, User's Guide and blister pack are included in this submission (attachment 1). Unless otherwise noted, the reviewer's comments and recommendations refer to the labeling for both the 2 mg and 4 mg drug products. Graphic specifications for the labeling were not included in this submission.

Stock Keeping Unit: (describe unit)
Cartons for the 2 mg 72 count, and 4 mg 72 count cartons

Reviewer's Comments
The sponsor has made the following changes to the Principal Display Panel:

1. The phrase "From the marketers of Nicorette®" is moved center above the brand name.
2. The phrase **"Better Tasting Mint Flavor"** is inserted on the top left corner of the front panel.
3. The word "NEW" is deleted from the carton front.
4. The pill icon on the carton front is enhanced by adding a series of circles and spokes around the pill.

These revisions are acceptable.

Reviewer's Recommendations

The sponsor needs to provide the graphic specifications used for the Drug Facts labeling (e.g., type and font sizes, bullet sizes, hairline sizes, barline sizes, etc.) in accordance with 21 CFR 201.66(d).

These comments can be conveyed to the sponsor.

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

7/1/03
Helen Cothran, B.S.
Team Leader, HFD-560

Item 2: Draft Labeling

The draft labeling for Spearmint Commit Lozenges is included in this section. With the exception of the addition of the wording "Better Tasting Mint Flavor" on the front panel and the additional inactive ingredients listed on back panels of the carton labels, there are no difference between this new draft labeling and the original flavor Commit Lozenge labeling.

Table of Contents
NDA 21-330
Commit Lozenge 2 & 4 mg
Supplemental New Drug Application
Item 2: Draft Labeling

*** N/A = No paper review copy included**

Note: Page numbers for each document are located in the lower left corner of each page.

Following this page, 22 pages withheld in full - draft labeling (b)(4)

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

/s/

Mary Robinson
7/2/03 03:22:55 PM
INTERDISCIPLINARY

Helen Cothran
7/2/03 05:14:05 PM
INTERDISCIPLINARY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021330/S-002

CHEMISTRY REVIEWS

Chemistry Review #1	**1. Division** HFD-560	**2. NDA/Supp. Number** 21-330/S-002
3. Name and Address of Applicant GlaxoSmithKline 1500 Littleton Road Parsippany, NJ 07054-3884		**4. Date of Original Supplement** **Submission** **Stamp** 3/12/03 3/14/03
5. Name of Drug Nicotine Polacrilex	**6. Nonproprietary Name** Nicotine	
7. Supplement Provides for: Spearmint flavored Commit® Lozenge.		**8. Amendment(s)** **User Fee** 10/15/03 2/16/04
9. Pharmacological Category	**10. How Dispensed** OTC	**11. Related Documents** None
12. Dosage Form: Lozenge	**13. Potency(ies):** 2 mg and 4 mg	
14. Chemical Name and Structure see USAN		

15. **Comments**:

The supplement was submitted as a pre-approval supplement (PAS).

The firm developed a new spearmint flavored product in an effort to better mask the taste. No other changes are involved in the ingredients. Manufacture (and the control) of the drug substance and the drug product remained the same.

The acceptance criteria for impurity (b) (4) (b) (4) which is currently approved.

A total of 4 batches, 1 pilot batch and 3 full production batches for 2 mg and 4 mg strengths were placed on stability. Twenty-four months of data was provided for the pilot scale batch and 18 months for the full production batches. Stability data on batches stored at 25°C/60% RH were within the proposed acceptance criteria. Some stability samples stored at 40°C/75% RH and 30°C/70% RH failed when stored up to 9 or 12 months.

16. Conclusions and Recommendations: Recommend Approval

17. Name	**Signature**	**Date**
Bart Ho Review Chemist		February 6, 2004

Doc ID: 21330S2NewflavorRv2App

Following this page, 4 pages withheld in full - (b)(4)

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

/s/

Bartholomew Ho
2/6/04 11:15:25 AM
CHEMIST

John Smith
2/6/04 12:34:11 PM
CHEMIST

Chemistry Review #1	**1. Division** HFD-560	**2. NDA/Supp. Number** 21-330/S-002
3. Name and Address of Applicant GlaxoSmithKline 1500 Littleton Road Parsippany, NJ 07054-3884		**4. Date of** **Subm.** **Review** **User Fee** 3/12/03 7/10/03 7/14/03
5. Name of Drug Nicotine Polacrilex	**6. Nonproprietary Name** Nicotine	
7. Supplement Provides for: A spearmint flavored Commit® Lozenge.		**8. Amendment(s)** N/A
9. Pharmacological Category	**10. How Dispensed** OTC	**11. Related Documents** None
12. Dosage Form: Lozenge	**13. Potency(ies):** 2 mg and 4 mg	
14. Chemical Name and Structure see USAN		

15. **Comments**:

The firm developed a new spearmint flavored product in an effort to better mask the taste. There are no other changes in the ingredients contained, no changes to the manufacture of the drug substance. The limit for the (b) (4) are not acceptable.

A total of 4 batches, 1 pilot batch and 3 full production batches for 2 mg and 4 mg strengths were placed on stability. Eighteen months of data was provided for the pilot scale batch and 12 months for the full production batches. Stability data on batches stored at 25°C/60% RH were within the proposed acceptance criteria. Some stability samples stored at 40°C/75% RH and 30°C/70% RH failed when stored up to 9 or 12 months.

16. Conclusions and Recommendations: Approvable with comments.

17. Name	**Signature**	**Date**
Bart Ho Review Chemist		July 14, 2003

Doc ID: 21330S2NEWFLAVORNA

Following this page, 9 pages withheld in full - (b)(4)

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

/s/

Bartholomew Ho
7/14/03 02:55:56 PM
CHEMIST

John Smith
7/14/03 03:04:58 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021330/S-002

PHARMACOLOGY AND TOXICOLOGY REVIEWS

Memo

To: Laura Shay, Division OTC Drug Products, HFD-560

From: R. Daniel Mellon, Ph.D., Supervisory Pharmacologist, HFD-170

Through: Bob Rappaport, M.D., Division Director, HFD-170

Date: February 11, 2004

Re: Division of Over the Counter Drug Products pharmacology/toxicology consultation on GlaxoSmithKline's Supplemental New Drug Application (S-002) Amendment under NDA 21-330 for a new spearmint flavored Commit® (nicotine polacrilex) Lozenge.

Background: GlaxoSmithKline (GSK) submitted a Supplemental New Drug Application for NDA 21-330 on March 12, 2003 for a new spearmint flavor that the sponsor intends to better mask the unpleasant taste of the nicotine replacement product. In addition, the supplement proposed to increase the drug product release and stability specifications for (b) (4) (a component of the previously unidentified peak (b) (4)). There were no changes in the limits in the drug substance for (b) (4) The Agency concluded that the supplement was approvable, however, there were several deficiencies, including the lack of safety data to support increasing the specifications for (b) (4)

Consultation Request: For the current consultation, DOTCDP is requesting a review of any pharmacology toxicology issues related to this prior approval supplement for a flavor change (spearmint).

In the Amendment to S-002 (October 15, 2003), GSK has set the specification limits for drug substance, drug product release and drug product stability to be identical to those currently approved for the original Commit® lozenge under the NDA.

Comments from HFD-170: The specifications for the drug substance, drug product release and drug product stability, as outlined in the October 15, 2003 letter, are acceptable. From the pharmacology/toxicology perspective, the supplement may be approved.

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

/s/

R. Daniel Mellon
2/11/04 01:29:11 PM
PHARMACOLOGIST

Bob Rappaport
2/11/04 02:49:21 PM
MEDICAL OFFICER

Memo

To: Laura Shay, Division OTC Drug Products, HFD-560

From: R. Daniel Mellon, Ph.D., Acting Supervisory Pharmacologist, HFD-170

Through: Bob Rappaport, M.D., Division Director, HFD-170

Date: September 12, 2003

Re: Division of Over the Counter Drug Products pharmacology/toxicology consultation on safety qualification of the impurity (b) (4) for NDA 21-330 Nicotine Polacrilex (Commit®) Lozenge (S-002).

Background: HFD-170 received and responded to a request for consultation from DOTCDP requesting clarification of the recommendations on the proposed increase in the drug product stability specification for (b) (4) in the 4 mg nicotine lozenge. Recommendations were previously submitted to DOTCDP in memos dated June 6, 2003 and July 24, 2003.

In an e-mail from David Schifkovitz (GlaxoSmithKline) dated 9/2/2003, he wrote:

> "Our most recent lozenge submission (NDA 21-330) included a qualification for (b) (4) (see attached section) that presented acute and genetic (Ames test) toxicology data as well as data demonstrating that (b) (4) is a metabolite of nicotine in several animal species and humans. Our analytical method for lozenge reports (b) (4) as part of a (b) (4), and toxicologist at FDA was very clear in the August 8th FAX that " (b) (4) in the 4 mg tablet (b) (4)%) is unacceptable".
>
> My question.....the analytical method for new gum measures (b) (4) (b) (4) is not present in gum at any level approaching identification or qualification. Given the above data for (b) (4) metabolite of nicotine and acute and genetic toxicology data)... is a specification limit of (b) (4) acceptable in 4 mg gum. This translates to 4 mg x 24 pieces/day max X (b) (4)% = (b) (4) per day."

In this consultation, DOTDP requests pharmacology/toxicology input regarding the above proposal by GSK.

The approved specifications for impurities/degradation products in the drug substance and drug product are listed in the table below (taken from Chemistry

Review #3 for NDA 21-330 by Dr. Mike Theodorakis dated October 24, 2002). The highlighted specification for (b) (4) stability of the 4 mg tablet has been proposed to be increased to (b) (4)**% w/w.**

Summary of Approved Drug Product Specifications (October 24, 2002):

Impurities/Degradation Products	Drug Substance	Drug Product			
		Release		Stability	
		2 mg	4 mg	2 mg	4 mg
(b) (4)					
Individual Unspecified Impurity					
Sum of all impurities					

The sponsor justifies this increase with the following arguments:

1. Acute toxicity and genetic toxicity studies have been reported for (b) (4)
2. (b) (4) human metabolite.

Conclusions: The justification for increasing the drug product specifications for (b) (4) is not acceptable. First, although acute toxicity and genetic toxicology studies have been reported in the literature, the genetic toxicology study indicates that (b) (4) tested positive in the *in vitro* chromosome aberrations study. As such, this positive finding does not qualify the safety of the impurity. Further qualification would be required to demonstrate the safety of the impurity.

Second, although (b) (4) metabolite of nicotine in humans ((b) (4)%), the clinical exposure to (b) (4) in the lozenge is via a different route than what occurs via metabolic production of (b) (4). Of specific concern is the increased exposure of the oral tissues, esophagus and stomach lining which do not normally come in contact to the same extend when (b) (4) is produced metabolically. Further, under acidic conditions (such as the stomach), (b) (4), which has tested positive in animal models of carcinogenicity. Based upon these findings, further qualification of (b) (4) would be required to increase the approved levels in the drug product.

Recommendations: The following recommendation should be relayed to the sponsor:

The proposed specification for (b) (4) of NMT (b) (4)% for the 4 mg lozenge (stability) is not acceptable. To increase the specifications, (b) (4) must be adequately qualified. Although (b) (4) metabolite of nicotine in humans, the exposure to (b) (4) in the lozenge is via a different route than via metabolism. Of specific concern are the oral tissues, esophagus and stomach lining which do not normally come in contact with (b) (4) produced metabolically (to the same extent). The literature suggests that (b) (4) tested positive in the *in vitro* sister chromatid exchange assay. Further, this compound can be (b) (4), which has tested positive in animal models of carcinogenicity. As such adequate qualification of (b) (4) would be required to support the proposed increase in the specifications. This initial qualification would normally be a minimal genetic toxicology screen (*in vitro* mutagenicity and *in vitro* chromosomal aberrations assay). The sponsor may either rely on the published literature which indicates that the compound tests positive as a clastogen, or reproduce these studies under GLP conditions. If you rely upon the published literature, further qualification of the positive response in the genetic toxicology study would be required. This could be completed via carcinogenicity assessment in a single species (either a 2-year rodent bioassay or a p53 transgenic mouse model). The sponsor is encouraged to submit carcinogenicity protocols to the Carcinogenicity Assessment Committee (CAC) for concurrence prior to initiation of these studies.

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

/s/

R. Daniel Mellon
9/17/03 11:25:50 AM
PHARMACOLOGIST

Bob Rappaport
9/17/03 12:01:24 PM
MEDICAL OFFICER

Memo

To: Laura Shay, Division OTC Drug Products, HFD-560

From: R. Daniel Mellon, Ph.D., Pharmacology Reviewer, HFD-170

Through: Timothy J. McGovern, Ph.D., Supervisory Pharmacologist, HFD-170 and Bob Rappaport, M.D., Acting Division Director, HFD-170

Date: July 24, 2003

Re: Division of Over the Counter Drug Products pharmacology/toxicology consultation on safety qualification of the new spearmint flavor and the proposed increased specifications for the impurity (b) (4) for NDA 21-330 Nicotine Polacrilex (Commit®) Lozenge (S-002).

Background: GlaxoSmithKline (GSK) submitted a Supplemental New Drug Application for NDA 21-330 on March 12, 2003 for a new spearmint flavor that the sponsor intends to better mask the unpleasant taste of the nicotine replacement product. In addition, the supplement proposed to increase the drug product release and stability specifications for (b) (4) (a component of the previously unidentified peak (b) (4)). There are no changes in the limits in the drug substance for (b) (4) HFD-170 received a request for consultation from DOTCDP requesting "review of any pharmacology toxicology issues related to this prior approval supplement for a flavor change (spearmint)."

NOTE: This supplement incorporates revised drug product specifications for (b) (4) which were submitted for review (b) (4) However, the sponsor subsequently submitted revised specifications (b) (4).

The approved specifications for impurities/degradation products in the drug substance and drug product are listed in the table below (taken from Chemistry Review #3 for NDA 21-330 by Dr. Mike Theodorakis dated October 24, 2002).

Summary of Approved Drug Product Specifications (October 24, 2002):

Impurities/Degradation Products	Drug Substance	Drug Product			
		Release		Stability	
		2 mg	4 mg	2 mg	4 mg
		(b) (4)			
Individual Unspecified Impurity					
Sum of all impurities					

(b) (4) **FLAVOR** (b) (4)

The proposed excipient list for the spearmint nicotine polacrilex lozenges is provided in the sponsor's table below:

Ingredient Name	Composition (mg/lozenge)	
	2 mg lozenge	4 mg lozenge
Nicotine Polacrilex (b) (4), USP	(b) (4)	
Mannitol, USP		
Sodium Alginate, NF		
Xanthan Gum, NF		
Potassium Bicarbonate, USP		
Calcium Polycarbophil, USP		
Sodium Carbonate, NF (b) (4)		
Aspartame, NF		
(b) (4) Flavor (b) (4)		
Magnesium Stearate NF		
Total lozenge weight	1260.000	1260.000

1 (b) (4)

According to the Sponsor, "The flavor, (b) (4) Flavor (b) (4) is certified by the manufacturer to comply with the requirements of the Food, Drug and Cosmetic Act and contains only ingredients which are listed as approved for use in a regulation of FDA, are listed as being generally recognized as safe on the FEMA GRAS lists, or are foods."

GSK indicated in the CMC section of the supplement that the (b) (4) Flavor (b) (4) (b) (4) is manufactured by (b) (4) and has an authorization letter attached to the supplement. The (b) (4) flavor is a (b) (4) and contains both natural and artificial components. No further information is provided to evaluate any pharmacology/toxicology concerns.

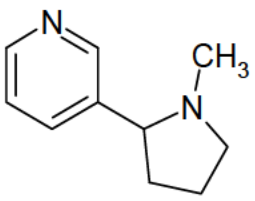
(b) (4)

In supplement 002 (b) (4), GSK proposed to increase the drug product stability specification for the (b) (4) to (b) (4)% for the 2 mg lozenge and (b) (4)% for the 4 mg lozenge. Both of these specifications were previously approved at a level of (b) (4)%. Based upon comments provided with (b) (4), the sponsor submitted revised specifications (b) (4). The revised specifications are listed in the table below (increases from approved levels are highlighted).

Summary of Revised Proposed Drug Product Specifications (b) (4)

Impurities/Degradation Products	Drug Substance	Drug Product			
		Release		Stability	
		2 mg	4 mg	2 mg	4 mg
(b) (4)					
Individual Unspecified Impurity					
Sum of all impurities					

(b) (4) was previously an unidentified component of the unidentified peak called (b) (4). The approved specifications for (b) (4) are as follows: Drug



Nicotine

(b) (4)

product release (b) (4)% and drug product stability (b) (4)%. (b) (4) was recently determined to be composed of (b) (4)

(b) (4)
(see Sponsor's figure below).

(b) (4)

(b) (4)

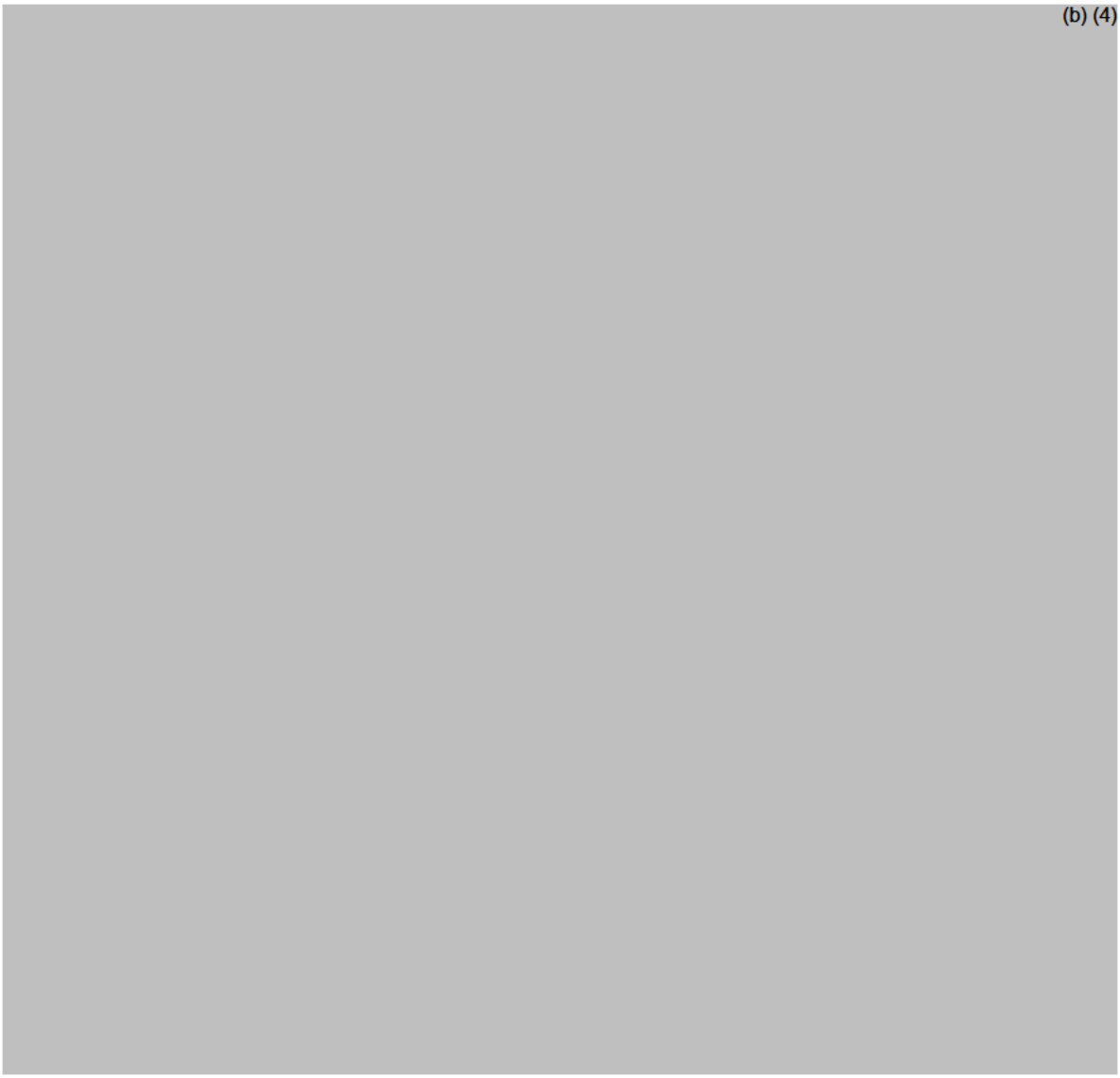
(b) (4)

GSK examined the biological safety of (b) (4) via a structure-activity analysis of (b) (4) using DEREK (Deductive Estimation of Risk from Existing Knowledge) version 6.0.0. This system examines the molecules for structural similarities to compounds with characterized mutagenicity, carcinogenicity, sensitization and irritation as well as other endpoints (developmental toxicology, teratogenicity, nephrotoxicity, hepatotoxicity, neurotoxicity, pulmonary toxicity and estrogenicity). The results suggested no alerts for (b) (4) (b) (4). However, an alert resulted for (b) (4)

.

A review of the literature supports the conclusion that (b) (4) may be a metabolite of nicotine. (b) (4) recently provided *in vitro* data supporting the conclusion that nicotine can be metabolized by (b) (4) to form

Following this page, 1 page withheld in full - (b)(4)



Conclusions: The justification for increasing the drug product specifications for (b) (4) is not acceptable. Specifically, adequate qualification of (b) (4) has not been provided. The proposed increase in drug product specifications above the approved and/or ICH recommended levels will require a minimal genetic toxicology screen (*in vitro* chromosome mutations assay and *in vitro* chromosome aberrations). Should (b) (4) produce a positive genetic toxicology response, the Sponsor should conduct additional qualification studies (e.g., $p53^{+/-}$ mouse assay) to support the proposed increase in drug product specifications.

Determination of the potential risk associated with the flavor change will require information regarding the content of the flavor (b) (4). No specific recommendations can be provided at this time.

Recommendations:

1. Information provided to support the proposed increase in drug product specifications for [redacted] is inadequate. Specifically, the sponsor proposes to set the drug product stability specification for [redacted] to [redacted]% for the 2 mg lozenge and [redacted]% for the 4 mg lozenge (see table 4.A.2.k-2). These specifications are greater than the previously approved specifications of [redacted]%. Due to the identified structural alert for mutagenic/carcinogenic potential associated with this compound, the sponsor should provide adequate safety qualification for the genotoxic potential of [redacted] (e.g., an *in vitro* point mutation study and an *in vitro* chromosomal aberration study) to support their proposed drug product stability specifications of [redacted]% and [redacted]%. Should [redacted] produce a positive genetic toxicology response; the sponsor should conduct additional qualification (e.g., a $p53^{+/-}$ mouse assay) to support the proposed increase in drug product specifications.

2. The sponsor's revised drug substance and drug product stability specification for [redacted] in the 2 mg lozenge ([redacted]% and [redacted]%, respectively) are acceptable.

3. The sponsor's revised drug product stability specification for [redacted] in the 4 mg tablet [redacted] is unacceptable. The current specification for the level of the 4 mg tablet is set at [redacted]%. Due to the identified structural alert for mutagenic/carcinogenic potential associated with this compound, the sponsor should provide adequate safety qualification for the genotoxic potential of [redacted] (e.g., an *in vitro* point mutation study and an *in vitro* chromosomal aberration study) to support their proposed drug product stability specification of [redacted]%. Should [redacted] produce a positive genetic toxicology response; the sponsor should conduct additional qualification (e.g., a $p53^{+/-}$ mouse assay) to support the proposed increase in drug product specifications.

4. Determination of the potential risk associated with the flavor change will require information regarding the content of the flavor [redacted] No specific recommendations can be provided at this time.

Reference List

[redacted]


(b) (4)

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

/s/

R. Daniel Mellon
8/8/03 12:43:35 PM
PHARMACOLOGIST

Timothy McGovern
8/12/03 07:38:39 AM
PHARMACOLOGIST
I concur.

Bob Rappaport
8/12/03 01:50:14 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021330/S-002

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-330
Submission Date: March 12, 2003
Drug Name:, Dose and Formulation: Nicotine Polacrilex Lozenges, 2 mg and 4 mg
Sponsor: GlaxoSmithKline, Parsippany, NJ 07054
Type of Submission: Supplemental NDA
Reviewer: Chandra S. Chaurasia, Ph. D.
Team Leader: E. Dennis Bashaw, Pharm. D.

I. SYNOPSIS:

Nicotine as a nicotine replacement therapy is available in many different formulations, such as polacrilex chewing gum (Nicorette), transdermal patch, inhaler , nasal spray and lozenge.

GlaxoSmithKline has approved mint-flavored nicotine lozenge marketed as Commit™ (NDA 21-330, Oct 31, 2002) Lozenge in 2- and 4-mg strength. In the current supplemental NDA 21-330, the firm is seeking approval of spearmint-flavored nicotine lozenges in 2- and 4-mg strength. The firm states that the proposed new spearmint flavored products will better mask the somewhat unpleasant taste of the mild mint-flavored Commit™ Lozenge.

As part of the development of this new formulation, the sponsor conducted a single dose 4-way crossover bioequivalence study (**S1740163**) of 2 mg and 4 mg nicotine lozenges comparing (b) (4) Spearmint and mint-flavored (b) (4) Original flavors.

No dissolution data are provided in the pharmacokinetic section of this supplemental NDA submission. It is being followed by the FDA chemist

Since the current supplemental NDA contains a single bioequivalence study comparing 2- and 4-mg spearmint lozenges with the currently marketed mint-flavored 2- and 4-mg lozenges, and the spearmint-flavored and mint-flavored formulations are identical except for the flavoring agent, a Question Based Review (QBR) format was not deemed necessary for this supplemental NDA.

II. RECOMMENDATIONS:

The supplemental NDA 21-330 is acceptable form the Clinical Pharmacology and Biopharmaceutics perspective. The in vitro dissolution issue is being followed by the FDA chemist.

Chandra S. Chaurasia, Ph.D. _____ Date:
Pharmacokinetics Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by E. Dennis Bashaw, Pharm.D. _____Date:

cc: NDA 21-330, HFD-560 (Div. File), HFD-660 CSO (Shay), HFD-880 (Bashaw), HFD-880 (Lazor), HFD-880 (Chaurasia)

III. STUDY S1740163:

Study Design: Open-Label, single-center, randomized, single dose, 4-way crossover.
Protocol Title: A four-way crossover, single-dose bioequivalence study of 2 mg and 4 mg nicotine lozenges comparing (b) (4) Spearmint and (b) (4) Original flavors.
Objectives: To compare (b) (4) Spearmint 2 mg and 4 mg nicotine lozenge with (b) (4) Original 2 mg and 4 mg nicotine lozenge, respectively to assess bioequivalence.
Principal Investigator: James C. Kisicki, MD.
Clinical Study Site: MDS Pharma Services, Lincoln, NE 68502.
Bioanalytical Laboratories: (b) (4)
Study Period: Start Date: 10/26/2001, Completion Date: 11/18/2001
Treatments and Administration:
Treatment A: (b) (4) Original 4 mg nicotine lozenge, Lot No. 9005FP1011, Exp. 02/28/02, manufactured by GlaxoSmithKline Consumer Healthcare (GSKCH).
Treatment B: (b) (4) Spearmint 4 mg nicotine lozenge, Lot No. 9029FP1003, Exp. 02/28/02, manufactured by GlaxoSmithKline Consumer Healthcare
Treatment C: (b) (4) Original 2 mg nicotine lozenge, Lot No. 9003FP1013, Exp. 02/28/02, manufactured by GlaxoSmithKline Consumer Healthcare.
Treatment D: (b) (4) Spearmint 2 mg nicotine lozenge, Lot No. 9028FP1003, Exp. 02/28/02, manufactured by GlaxoSmithKline Consumer Healthcare.

The study was comprised of 4 study sessions, each lasting approximately 24 hours. Each session was separated by an inter-dose washout period of at least 24 hours. Subjects were required to abstain from smoking for a minimum of 12 hours prior to drug administration, and were not permitted to resume smoking until the completion of all sampling for each study session. Subjects fasted for a minimum of 8 hours prior to dosing and for two hours after the drug administration and then consumed the standardized meals until the last pharmacokinetic sampling was done. The subjects were required to move the study drugs from side-to-side in their mouth once every 4 seconds until dissolved.

Study Population: Healthy male and female volunteers. A total of 40 subjects, (18 males, and 22 females; 38 Caucasian, 1 African-American, and 1 American Indian) were enrolled in the study, and 35 subjects, 16 males and 19 females: completed the study. Age (mean±SD, range) 32±11years (19-55 years).

Subjects' Inclusion and exclusion criteria are described in Vol. 2.0, pp. 36-38. Briefly inclusion criteria include smoking status (subjects who smoke 15 or more cigarettes per day and had a plasma cotinine level > 100 ng/mL at screening).

Analytical Methodology
Plasma Sampling Time**s:** blood samples were collected at 0 hour (predose), at 1, 1.5, 2, 3, 4, 6, 8 and 12 hours post-dose.
Assay Method: LC/MS/MS, Validation Summary provided in Vol. 2, pages 90-96.
Assay Sensitivity: LOQ of 1 ng/mL for nicotine. Assay was linear in the range of 1-50 ng/mL for nicotine.
Quality control samples analyzed with each analytical run had coefficients of variation less than or equal to 14.92%.
Accuracy and Precision: Between-run accuracy ranged from -0.5 to 5.4%, and the precision ranged from 3.2 to 8.4%.

Results: The mean ± SD nicotine plasma concentration-time curves and PK parameters of the 4-mg and 2-mg [redacted] Spearmint Nicotine Lozenges and [redacted] Original Nicotine Lozenges are summarized in Tables 1 and 2, respectively and Figure 1 in Appendix. Eleven of the 35 subjects who completed the study had baseline nicotine concentrations greater than 5% of their respective Cmax values and, were thus excluded from the statistical analyses.
The mean Tmax of nicotine was approximately 1 hr for the 4-mg [redacted] Spearmint and [redacted] Original Lozenges, and 0.8 hr for the respective 2-mg lozenges. The half-lives for all the 4 formulations were in the range of 1.84 to 2.02 hr. The 90% confidence intervals for the lnCmax, lnAUC0-t, and lnAUC0-inf for the test 2- and 4-mg lozenges were in the range of 91-106% with the point ratios between 0.977 to 0.990.

Table 1. Summary of the pharmacokinetic parameters of plasma nicotine for 4-mg [redacted] Spearmint Nicotine Lozenges and 4-mg [redacted] Original Nicotine Lozenges

	Treatment B*		Treatment A*			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI**	% Mean Ratio B/A**
Cmax ng/mL	8.676	1.924	8.861	2.09		
AUC0-t ng•h/mL	25.51	5.848	25.98	6.40		
AUC0-∞ ng•h/mL	29.58	6.494	30.00	6.34		
tmax (h)	1.08	0.63	1.15	0.55		
$t_{1/2}$ (h)	1.92	0.471	1.86	0.39		
Ke (h^{-1})	0.382	0.094	0.392	0.05		
lnCmax	2.136	0.228	2.154	0.247	92.5-105.8	98.0
lnAUC0-t	3.212	0.240	3.228	0.248	91.5-104.3	97.7
lnAUC0-∞	3.363	0.226	3.380	0.208	92.0-105.8	98.7

**Treatment B =* [redacted] *Spearmint Nicotine Lozenge, 1x4 mg.*
**Treatment A =* [redacted] *Original Nicotine Lozenges, 1x 4 mg*
***Based on LS means*

Table 2. Summary of the pharmacokinetic parameters of plasma nicotine for 2-mg [redacted] Spearmint Nicotine Lozenges and 2-mg [redacted] Original Nicotine Lozenges

	Treatment D		Treatment C			
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	90% CI*	% Mean Ratio B/A**
Cmax ng/mL	5.225	1.10	5.368	1.45		
AUC0-t ng•h/mL	12.87	3.48	13.21	4.06		
AUC0-∞ ng•h/mL	16.71	3.78	17.25	4.44		
tmax (h)	0.75	0.25	0.80	0.33		
$t_{1/2}$ (h)	1.94	0.65	2.02	0.80		
Ke (h^{-1})	0.389	0.108	0.374	0.091		
lnCmax	1.631	0.221	1.642	0.290	93.2-104.6	98.7
lnAUC0-t	2.519	0.279	2.534	0.320	92.7-105.7	99.0
lnAUC0-∞	2.790	0.236	2.814	0.274	92.0-105.4	98.5

**Treatment D =* [redacted] *Spearmint Nicotine Lozenge, 1x2 mg.*
**Treatment C =* [redacted] *Original Nicotine Lozenges, 1x2 mg*
***Based on LS means*

Safety Results:
As stated by the firm, a total of 110 adverse events were reported by 26 of the 40 subjects (65%) subjects experienced adverse events. Dyspepsia (20 events/9 subjects) and headache (18 events/7 subjects) were the most common AEs. All AEs were considered to be mild or moderate

in severity. No serious AEs were reported, and no subjects were discontinued from the study due to AEs. The investigator considered 93 (85%0 of the 110 events to be drug-related).

Fewer AEs were experienced following (b) (4) Spearmint 4mg compared with (b) (4) Original 4 mg (21% versus 39%, respectively). Similarly, fewer AEs were experienced following (b) (4) Spearmint 2 mg compared with (b) (4) Original 2 mg (15% versus 25%, respectively).

Comments:

1. The 90% confidence intervals for the ratios of Cmax, AUC_{0-t}, and $AUC_{0-\infty}$ for the two test formulations (b) (4) Spearmint 2 and 4-mg were within the acceptable limits of 80% to 125%.
2. Cotinine the major metabolite in plasma was not measured, however, this is not an essential information that needs to be obtained.
3. The bioequivalence study conducted by the firm comparing its spearmint-flavored nicotine polacrilex 2- mg and 4-mg (b) (4) lozenges to the respective mint-flavored reference products 2- and 4-mg (b) (4) Original lozenges (Commit™) following single oral dose administration under fasting condition is acceptable. The study demonstrates that the test 2- and 4-mg spearmint-flavored nicotine polacrilex lozenges are bioequivalent to the respective reference products Commit 2- and 4-mg Lozenges manufactured by GlaxoSmithKline.

Formulation:

The firm has provided the following qualitative formulation components for the 2- and 4-mg of the Test products, (b) (4) spearmint-flavored lozenges (Vol. 2, page 45):
The components of the (b) (4) Spearmint 2 mg and 4 mg Formulations

Nicotine Polacrilex, USP
Mannitol, USP
Sodium Alginate, NF
Xanthan Gum, NF
Potassium Bicarbonate, USP
Calcium Polycarbophil, USP
Sodium Carbonate, NF (b) (4)
Aspartame, NF
(b) (4) Flavor (b) (4)
Magnesium Stearate, NF
(b) (4)
Total Weight

The components and composition of the original mint-flavored 2- and 4-mg Commit Lozenges are provided in Table 3 in Appendix.

Comments on Formulation:

The compositions for the test products are not provided in the pharmacokinetic sections of the sNDA 21-330 submission. Nevertheless, it is noted that the firm states that the formulation of spearmint flavored Commit (nicotine polacrilex) lozenges 2- and 4-mg are identical to those of the original approved mint flavored Commit lozenges, 2- and 4-mg, respectively except for the flavoring agents.

Dissolution:
No dissolution data are provided in the pharmacokinetic section of this supplemental NDA submission. It has been noted and being followed by the FDA chemist.

Labeling Claims: None (OTC)

IV. RECOMMENDATIONS

The supplemental NDA 21-330 is acceptable form the Clinical Pharmacology and Biopharmaceutics perspective. The in vitro dissolution issue is being followed by the FDA chemist.

Appendix:

Figure 1.: Mean Plasma Nicotine Concentrations Versus Time

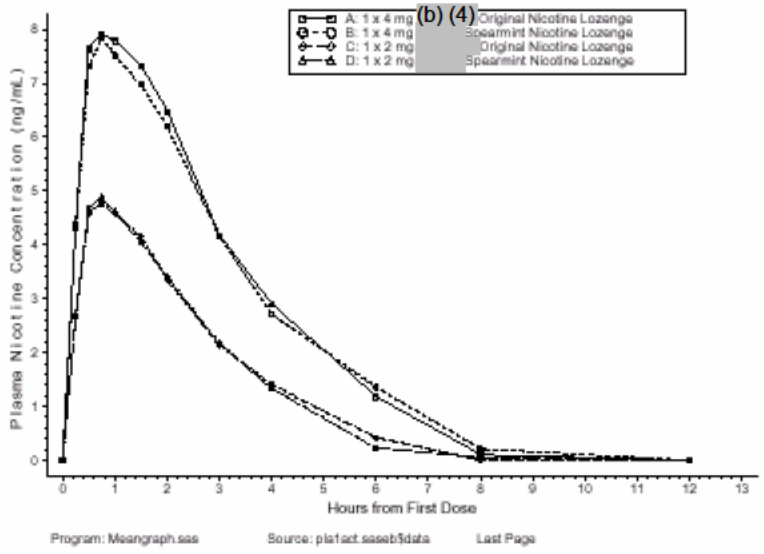


Table 3. The components and composition of the original mint-flavored 2- and 4-mg Commit Lozenges are provided below:

Ingredients	Composition (mg/lozenge)	
	2 mg strength	4 mg strength
(b) (4)		
Total Weight	1200.00	1200.00

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

/s/

Chandra S. Chaurasia
7/15/03 05:48:49 PM
BIOPHARMACEUTICS

Dennis Bashaw
7/15/03 05:51:58 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021330/S-002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Div. of Pharmaceutical Evaluation III
HFD- 880
BioPharm

FROM:
Laura Shay, PM
Div. OTC drug products: HFD-560

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10/28/03		21-330	SCS supplement: resubmission following an AE letter	October 17, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nicotine Polacrilex (Commit) Lozenge			February 1, 2004

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- **X** RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	**X** CHEMISTRY REVIEW ☐ PHARMACOLOGY **X** BIOPHARMACEUTICS OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the Biopharm issues related to this re-submission of a prior approval supplement for a flavor change (spearmint) for Commit® Lozenge.

The supplement was submitted electronically and is located in the electronic document filing room (EDR).

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Curtis Rosebraugh

10/28/03 12:29:51 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Div. of Anesthetic, Critical Care, and Addiction Drug: HFD-170
PharmTox

FROM:
Laura Shay, PM
Div. OTC drug products: HFD-560

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10/28/03		21-330	SCS supplement: resubmission following an AE letter	October 17, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nicotine Polacrilex (Commit) Lozenge			February 1, 2004

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- **X** RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	**X** CHEMISTRY REVIEW ☐ PHARMACOLOGY BIOPHARMACEUTICS **X** OTHER (SPECIFY BELOW): **Pharmtox**

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the Pharmtox issues related to this re-submission of a prior approval supplement for a flavor change (spearmint) for Commit® Lozenge.
The supplement was submitted electronically and is located in the electronic document filing room (EDR).

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Curtis Rosebraugh

10/28/03 12:25:24 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Division of OTC Drug Products
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: September 24 , 2003

To: Dave Schifkovitz	**From:** Laura Shay, MS, RN, C-ANP Regulatory Project Manager
Company: GlaxoSmithKline	Division of Over-the-Counter Drug Products
Fax number: 973-889-2244	**Fax number:** (301) 827-2315
Phone number: 973-889-2509	**Phone number:** (301) 827-2274

Subject: Comments from Pharmtox re: NDA 21-330

Total no. of pages including cover: 2

Document to be mailed: ❑ YES ☑ NO

Please refer to your supplemental new drug application NDA 21-330, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Commit® Lozenge.

We also refer to your e-mail sent to us on September 2, 2003.

We have attached reviewer's comments. If you have any questions you may refer them to Laura Shay, Regulatory Project Manager at (301) 827-2274.

Pharmtox Recommendations:

The proposed specification for (b) (4) of NMT (b) (4)% for the 4 mg lozenge (stability) is not acceptable. To increase the specifications, (b) (4) must be adequately qualified. Although (b) (4) metabolite of nicotine in humans, the exposure to (b) (4) in the lozenge is via a different route than via metabolism. Of specific concern are the oral tissues, esophagus and stomach lining which do not normally come in contact with (b) (4) produced metabolically (to the same extent). The literature suggests that (b) (4) tested positive in the *in vitro* sister chromatid exchange assay. Further, this compound can be (b) (4) which has tested positive in animal models of carcinogenicity. As such adequate qualification of (b) (4) would be required to support the proposed increase in the specifications. This initial qualification would normally be a minimal genetic toxicology screen (*in vitro* mutagenicity and *in vitro* chromosomal aberrations assay). The sponsor may either rely on the published literature which indicates that the compound tests positive as a clastogen, or reproduce these studies under GLP conditions. If you rely upon the published literature, further qualification of the positive response in the genetic toxicology study would be required. This could be completed via carcinogenicity assessment in a single species (either a 2-year rodent bioassay or a p53 transgenic mouse model). The sponsor is encouraged to submit carcinogenicity protocols to the Carcinogenicity Assessment Committee (CAC) for concurrence prior to initiation of these studies.

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

/s/

Laura Shay
9/24/03 03:26:45 PM
UNKNOWN

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Div. of Anesthetic, Critical Care, and Addiction Drug Prod.
HFD-170
PharmTox

FROM:
Laura Shay, PM
Div. OTC drug products: HFD-560

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
9/11/03		21-330	e-mail	August 28, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nicotine Polacrilex (Commit) Lozenge			September 12,2003

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- X FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS X OTHER (SPECIFY BELOW): PharmTox

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the Pharmtox issues related to (b) (4) submitted in the attached pfd file sent by GalxoSmithKline and provide comment.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Following this page, 2 pages withheld in full - (b)(4)

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

/s/

Curtis Rosebraugh
9/12/03 08:40:00 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Division of OTC Drug Products
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: August 8, 2003

To: Dave Schifkovitz	**From:** Laura Shay, MS, RN, C-ANP Regulatory Project Manager
Company: GlaxoSmithKline	Division of Over-the-Counter Drug Products
Fax number: 973-889-2244	**Fax number:** (301) 827-2315
Phone number: 973-889-2509	**Phone number:** (301) 827-2274

Subject: Comments from Pharmtox re: NDA 21-330 /S002

Total no. of pages including cover: 2

Document to be mailed: ❑ YES ☑ NO

Please refer to your supplemental new drug application NDA 21-330 (b) (4) (b) (4) Supplement 002 dated March 14, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Commit® Lozenge.

(b) (4)

We have attached reviewer's comments related to Supplement 002 (b) (4) (b) (4). If you have any questions you may refer them to Laura Shay, Regulatory Project Manager at (301) 827-2274.

1. Information provided to support the proposed increase in drug product specifications for (b) (4) is inadequate. Specifically, the sponsor proposes to set the drug product stability specification for (b) (4) to (b) (4)% for the 2 mg lozenge and (b) (4)% for the 4 mg lozenge (see table 4.A.2.k-2). These specifications are greater than the previously approved specifications of (b) (4)%. Due to the identified structural alert for mutagenic/carcinogenic potential associated with this compound, the sponsor should provide adequate safety qualification for the genotoxic potential of (b) (4) (e.g., an *in vitro* point mutation study and an *in vitro* chromosomal aberration study) to support their proposed drug product stability specifications of (b) (4)% and (b) (4)%. Should (b) (4) produce a positive genetic toxicology response; the sponsor should conduct additional qualification (e.g., a $p53^{+/-}$ mouse assay) to support the proposed increase in drug product specifications.

2. The sponsor's revised drug substance and drug product stability specification for (b) (4) in the 2 mg lozenge ((b) (4)% and (b) (4)%, respectively) are acceptable.

3. The sponsor's revised drug product stability specification for (b) (4) in the 4 mg tablet ((b) (4)%) is unacceptable. The current specification for the level of the 4 mg tablet is set at (b) (4)%. Due to the identified structural alert for mutagenic/carcinogenic potential associated with this compound, the sponsor should provide adequate safety qualification for the genotoxic potential of (b) (4) (e.g., an *in vitro* point mutation study and an *in vitro* chromosomal aberration study) to support their proposed drug product stability specification of (b) (4)%. Should (b) (4) produce a positive genetic toxicology response; the sponsor should conduct additional qualification (e.g., a $p53^{+/-}$ mouse assay) to support the proposed increase in drug product specifications.

4. Determination of the potential risk associated with the flavor change will require information regarding the content of the flavor (b) (4). No specific recommendations can be provided at this time.

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

/s/

Laura Shay
8/8/03 01:50:31 PM
UNKNOWN

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-330/S-002

GlaxoSmithKline Consumer healthcare
Attention: David Schifkovitz
Director of Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Mr. Schifkovitz:

Please refer to your supplemental new drug application dated March 12, 2003, received March 14, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Commit Lozenge (Nicotine Polacrilex, USP) 2 mg and 4 mg.

This supplemental new drug application provides for a spearmint flavored lozenge.

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

1. (b) (4)
2.
3.
4.
5.
6.
7.

8. Information on (b) (4) was not found in DMF # (b) (4). We have requested the DMF holder to provide the appropriate information.

Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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.

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

Sincerely,

{See appended electronic signature page}

John Smith, Ph.D.
Chemistry Team Leader
Division of New Drug Chemistry III
Center for Drug Evaluation and Research

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

/s/

John Smith
7/14/03 05:02:25 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Div. of Pharmaceutical Evaluation III
HFD- 880
BioPharm

FROM:
Laura Shay, PM
Div. OTC drug products: HFD-560

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3/05/03		21-330	SCS suppl.	March 12, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nicotine Polacrilex (Commit) Lozenge			June 30, 2003

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- X FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY X BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review any of the Biopharm issues related to this prior approval supplement for a flavor change(spearmint).
The supplement was submitted electronically and is located in the electronic document filing room (EDR).

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Curtis Rosebraugh
3/27/03 10:38:00 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Div. of Anesthetic, Critical Care, and Addiction Drug Prod.
HFD-170
PharmTox

FROM:
Laura Shay, PM
Div. OTC drug products: HFD-560

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3/05/03		21-330	SCS suppl.	March 12, 2003

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Nicotine Polacrilex (Commit) Lozenge			June 30, 2003

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- X FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS X OTHER (SPECIFY BELOW): PharmTox

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review any of the Pharmtox issues related to this prior approval supplement for a flavor change(spearmint).
The supplement was submitted electronically and is located in the electronic document filing room (EDR).

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Curtis Rosebraugh
3/27/03 10:37:04 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-330/S-002

PRIOR APPROVAL SUPPLEMENT

GlaxoSmithKline Consumer Healthcare
Attention: Joseph Kiceina
Associate Director, Regulatory Affairs
1500 Littleton Road
Parsippany, NJ 07054-3884

Dear Mr. Kiceina:

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: Commit (2 mg and 4 mg nicotine polacrilex) Lozenge

NDA Number: 21-330

Supplement number: 002

Date of supplement: March 12, 2003

Date of receipt: March 14, 2003

This supplemental application proposes an additional formulation under the tradename Commit Spearmint and an increase in drug product limits for (b) (4) in release and stability specifications.

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 May 13, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 14, 2003.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Over-the-Counter Drug Products, HFD-560
Attention: Division Document Room HFD-560
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Over-the-Counter Drug Products, HFD-560
Attention: Division Document Room HFD-560
9201 Corporate Blvd
Rockville, Maryland 20850-3202

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

Sincerely,

{See appended electronic signature page}

David Hilfiker
Chief, Project Management Staff
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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

/s/

David Hilfiker

3/27/03 01:51:58 PM