CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-360

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-360
Submission Code	N-000
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Reviewer Name	Priscilla Callahan-Lyon, MD
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Established Name	Nicotine Polacrilex
(Proposed) Trade Name	Nicorette®
Therapeutic Class	Smoking Cessation Therapy
Applicant	GlaxoSmithKline
Priority Designation	S
Formulation	Lozenge
Dosing Regimen	If you smoke your first cigarette within 30 minutes of waking up use 4 mg nicotine lozenge according to the below 12 week schedule: If you smoke your first cigarette more than 30 minutes after waking up use 2 mg nicotine lozenge according to the below 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

Indication	Reduces withdrawal symptoms, including nicotine craving associated with quitting smoking
Intended Population	Current Cigarette Smokers ages 18 and over

Table of Contents

EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The proposed new formulation for nicotine polacrilex lozenges, Nicorette lozenge 2 mg and 4 mg is acceptable. The new formulation is the same active ingredient and has the same dosing instructions and indications as the currently marketed Commit lozenge. The product has already been shown to be efficacious and safe. There are no new efficacy data and the safety update reveals no new concerns. The recommended regulatory action is approval.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No special postmarketing risk management activities are recommended.

1.2.2 Required Phase 4 Commitments

No additional requirements are recommended.

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

GlaxoSmithKline (GSK) is submitting this New Drug Application to provide a smaller version of the currently available nicotine polacrilex lozenge, Commit. The new lozenges, Nicorette® 2 mg and 4 mg, are considered by GSK to be a line extension of the currently marketed Commit Lozenges which are available in the same strengths and contain the same active ingredient, nicotine polacrilex. The indication is identical to the currently approved Commit Lozenges; "reduces withdrawal symptoms, including nicotine craving associated with quitting smoking." One attribute that some consumers find unappealing is the actual size of the current lozenge. At [redacted] the lozenge is quite large and takes some time to dissolve. The new formulation is only [redacted] It is smaller and dissolves more quickly. b(4)

The sponsor has not made it clear if the currently marketed Commit lozenge will remain on the market if the new formulation is approved. It is also not clear if the name of the Commit lozenge will be changed to Nicorette. FDA has requested GSK to clarify these issues but the response is pending.

The sponsor conducted two *in vivo* bioequivalence studies comparing the new product to the current Commit lozenge. These two studies, S3010445 and S3010446, were discussed with FDA at a meeting on 1/29/08. Based on the discussion, GSK conducted an additional bioequivalence study (S3010567) which forms the basis of this submission.

1.3.2 Efficacy

There are no new efficacy data in this NDA submission. The efficacy of the marketed lozenge formulation was established in the pivotal safety and efficacy study (S1410043) in the approved original NDA 21-330. Study S3010567 indicated bioequivalence to the marketed Commit lozenge for both the 2 mg and 4 mg product and further efficacy study was felt not to be needed.

1.3.3 Safety

Safety data to support this NDA comes from adverse event reports from the Phase I studies (S2300319, S2300339, and S2300320) and the Phase II studies (S3010445, S3010466, and S3010567). In addition, an extensive review of postmarketing safety data done by GSK particularly focused on the use of the nicotine replacement products in pregnant and nursing women and the use, misuse, and abuse of the products by all users and by adolescents under age 18. A concern was raised that more rapid dissolution of the Nicorette lozenge may result in higher oral cavity nicotine level and possibly increased side effects. FDA requested that the sponsor address this issue as well.

The Phase I pharmacokinetic studies were done using a different formulation of the smaller lozenge. The active ingredient is the same (nicotine polacrilex) but the exact formulation is different from the proposed product. The information obtained from these studies was reviewed for adverse events, safety, and extent of exposure. Of the 233 subjects enrolled in the Phase I studies, 134 received lozenges. A total of 36 patients in the Phase I studies received a 2 mg lozenge and 6 (16.7%) had an adverse event considered to be treatment related. A total of 56 subjects in the Phase I studies received a 4 mg lozenge and 5 (9%) experienced a treatment related adverse event. There were 42 patients in study S2300339 that received thirteen doses of the 1.5 mg lozenge and 43% had an event possibly or probably related to treatment. The subjects in the other studies only received single doses of the lozenge. The most common adverse events noted in the Phase I studies were gastrointestinal symptoms, dizziness, and headache. None of the adverse events were serious. Most of the adverse events reported in the Phase I studies were in Study S2300339 (the multi-dose study). There were no unexpected or unlabeled adverse events.

A total of 248 patients were evaluated in the Phase II studies. There were 66 subjects treated with the 2 mg Nicorette lozenge and 4.5% of subjects reported at least one treatment related

adverse event. There were 63 subjects treated with the 2 mg Commit lozenge and 6.3% of subjects reported at least one treatment related adverse event. There were 119 patients that received the 4 mg dose (58 received Nicorette and 61 received Commit). Of these, 24.1% of subjects treated with the 4 mg Nicorette lozenge, and 14.8% of subjects treated with the 4 mg Commit lozenge reported at least one treatment related adverse event. The most commonly reported treatment related adverse events (reported by >2 subjects) in the 4 mg Nicorette lozenge group were dizziness (3 subjects, 5.2%), headache (4 subjects, 6.9%), and nausea (6 subjects, 10.3%). None of the adverse events were considered serious. In the 4 mg Commit lozenge group, the most commonly reported adverse event was nausea (3 subjects, 4.9%). No adverse events were reported by more than 2 subjects in the 2 mg Nicorette lozenge or 2 mg Commit lozenge groups.

The incidence of adverse events was low and most were mild in intensity. The Nicorette lozenge had an incidence similar to the Commit lozenge. The most common adverse events noted in the studies were nausea and gastrointestinal symptoms, headache, dizziness, and dry mouth and these events appeared to be dose related, i.e. occurring in greater frequency with the 4 mg dose than the 2 mg dose. There were no unexpected or unlabeled adverse events.

A review of postmarketing safety data done by GSK particularly focused on the use of the nicotine replacement products in pregnant and nursing women and the use, misuse, and abuse of the products by all users and by adolescents under age 18. The GSK Worldwide Adverse Event Database was searched for all reports with a data lock point of 31 August, 2008. The nature of reported events is consistent with the product label. Gastrointestinal disorders were the most common followed by psychiatric disorders and respiratory, thoracic, and mediastinal disorders. Misuse or abuse by adolescents was rare. Of 19,202 events reported for nicotine gum, 37 cases were in adolescents ages 12 to 17. There were 11,181 reported events for the lozenge and 9 of these were in adolescents.

All reports received through the World Health Organization database (through September 2008) were reviewed. There were 982 reports for nicotine gum and 637 for the lozenge. Gastrointestinal and psychiatric events were the most common. The FDA AERS database was searched for all reports for Nicorette and Commit up to quarter 1 of 2008. There were 9409 reports for nicotine gum and 3274 reports for nicotine lozenge. The most commonly reported adverse events were gastrointestinal, psychiatric, and general disorders.

Data from the American Association of Poison Control Centers (AAPCC) was reviewed from 1997 to 2006. This data was for nicotine products in general – distinguishing the product type was not possible. The 2006 data from AAPCC showed a total of 924 exposures to a nicotine product; 698 of these were "unintentional." The formulation of the product was not specified and age information is limited in these reports. GSK performed a review of the Drug Abuse Warning Network website and found no mention of nicotine among the drug substances included in its reports.

The extent of exposure for the nicotine polacrilex gum and lozenge has been extensive. As of 31 August 2007, GSK estimates exposure to nicotine gum at ——— patients. Exposure to the b(4)

lozenge is even more extensive with estimates of [redacted] patients as of 31 August 2008. The integrated safety review found no unexpected adverse events or unusual findings. b(4)

There were no specific studies to assess the more rapid dissolution time and the possibility of associated increased side effects. The sponsor states the Nicorette lozenge, as with the Commit lozenge, is intended to be moved around the mouth until completely dissolved. GSK believes that the movement around the mouth will disperse the nicotine and decrease the likelihood of an area of increased local concentration. In addition, the sponsor believes that if such an increase did have an impact on the tolerability of the new product this would likely be seen as reports of adverse events related to the mouth or throat or possibly the gastrointestinal tract (if swallowing of nicotine was an issue).

Review of adverse events from the Phase II studies show relatively few incidences of problems related to the mouth or throat. Of events possibly related to swallowing of nicotine there was one report of hiccups for both the 2 mg and 4 mg Nicorette lozenge but none for either dose of Commit. Only for nausea was there an apparent difference between the Nicorette lozenge and Commit; with 7 reports (about 12% of subjects) for 4 mg Nicorette lozenges and 3 reports (about 5% of subjects) for Commit.

The sponsor believes that taken together this slight increase in reports of hiccups and nausea may suggest a slight increase in the proportion of nicotine swallowed for the Nicorette lozenge compared to Commit. However, this difference is unlikely to be major as the products are bioequivalent; if a significant proportion of the nicotine was being absorbed via a different route (i.e. through the gut rather than buccally) a difference in pharmacokinetic profile would have been seen between the two formulations. Both nausea and hiccups are included as potential adverse effects in the proposed labeling for the Nicorette lozenge. No new adverse events unique to the Nicorette lozenge formulation were identified. The more rapid dissolution time does not seem to be of clinical concern.

1.3.4 Dosing Regimen and Administration

The intended population for the 2 mg dose of Nicorette is patients that smoke their first cigarette of the day more than 30 minutes after awakening. The 4 mg dose is to be used by patients that smoke their first cigarette of the day within 30 minutes of waking up.

Once the correct dose size of the gum is established, patients are instructed to gradually use less of the nicotine replacement therapy according to the schedule below. Patients are advised not to smoke while using the lozenge and the goal is complete smoking cessation.

Table 1: Dosing Regimen for Nicorette 2 mg and 4 mg

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

1.3.5 Drug-Drug Interactions

There were no additional data submitted in regards to drug-drug interactions. It is known that smoking can interfere with the absorption of several medications and stopping smoking may consequently make some medications more (or less) effective and a dose adjustment may be required. The serum nicotine levels after smoking are generally higher than after using nicotine replacement products so these medications may blunt the effect of smoking cessation to some degree. Package labeling for Nicorette appropriately directs consumers to talk with their physician or pharmacist is they take medication for asthma or depression.

1.3.6 Special Populations

There have been no additional studies on special populations included with this submission. Use of nicotine replacement products is not recommended in pregnant or nursing women. There is no evidence of a need for dose adjustment in those over age 60 though the studies in this population are limited. The nicotine replacement products are not recommended for those under age 18.

This submission only deals with a change the size of the lozenge. The active ingredient, indication, dosage form, and route of administration are unchanged. There were no clinical studies submitted and none requested. This submission does not trigger the Pediatric Research Equity Act (PREA) though future studies on the efficacy of nicotine replacement product in adolescents would be useful.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

This New Drug Application is to provide for a smaller version of Nicotine Polacrilex Lozenges, 2 mg and 4 mg, currently marketed by GlaxoSmithKline (GSK) under an approved NDA 21-330 as Commit®. The new lozenges, Nicorette® 2 mg and 4 mg, are considered by GSK to be a line extension of the currently marketed Commit Lozenges (original, mint and cherry flavor) which are available in the same strengths and contain the same active ingredient, Nicotine Polacrilex. The indication is identical to the currently approved Commit Lozenges; "reduces withdrawal symptoms, including nicotine craving associated with quitting smoking." One attribute that some consumers find unappealing is the actual size of the current lozenge. At ——— the lozenge is quite large, takes some time to dissolve, and is less discreet for individuals who use the product throughout the day in a public setting. The new formulation is only ——— it is smaller and dissolves more quickly. b(4)

The sponsor conducted two *in vivo* bioequivalence studies comparing the new product to the current Commit lozenge. These two studies, S3010445 and S3010446, were discussed with FDA at a meeting on 1/29/08. Based on the discussion, GSK conducted an additional bioequivalence study (S3010567) which forms the basis of this submission. During the course of development of the Commit mini-lozenge, GSK evaluated multiple strengths of the product (1.5 mg, 2 mg, and 4 mg). The 1.5 mg dose was evaluated as part of a European initiative ——— The data from the Phase I trials that investigated the 1.5 mg mini-lozenge are considered as supportive for the current application with regards to extent of exposure and safety. b(4)

2.2 Currently Available Treatment for Indications

There are currently several therapies available for smoking cessation. In addition to the Commit lozenge, nicotine polacrilex is available as a gum and nicotine is also available as a slow release patch, a nasal spray, and an oral inhalation device. The nasal spray and inhaler are prescription products. The lozenge and the gum are available in several flavors and are OTC products. There are two other prescription products, varenicline and bupropion, that are approved therapies for smoking cessation.

2.3 Availability of Proposed Active Ingredient in the United States

The nicotine replacement products have been available in the United States since 1984. Nicotine polacrilex was initially approved in the gum form as a prescription product in 1984. It was made an OTC product in 1996 and has since been marketed in several flavors. Nicotine as a slow release patch formulation was approved as a prescription product in 1991 and was switched to OTC marketing in 1997. Commit lozenges were approved for OTC marketing in 2002 and is

also available in several flavors. Nicotine replacement is also available by prescription as a nasal spray and an inhaler.

2.4 Important Issues With Pharmacologically Related Products

The smoking cessation products have had several label changes over the years. Initially all nicotine replacement therapies were prescription products. When the nicotine replacement products were switched to OTC, sales were limited to locations where the age of the purchaser could be confirmed. Over the counter sale is restricted to patients age 18 and older. Patients are advised not to smoke cigarettes while using nicotine replacement products.

There have not been conclusive efficacy studies for the use of nicotine replacement products by patients under age 18. Patients with cardiac problems are advised to discuss use of the nicotine products with their physician but the medications are believed to be safer than smoking. Pregnant women or those that are breast feeding an infant are advised not to smoke. Use of smoking cessation therapy is controversial in this patient group. There is concern about the safety of nicotine exposure for unborn children and nursing infants when their mothers use nicotine replacement therapy.

2.5 Presubmission Regulatory Activity

A meeting with GSK was held January 9, 2008 regarding the smaller lozenges. At that time, GSK requested to submit a reformulated "mini-lozenge" as a supplement under the original Commit® NDA (21-330). GSK proposed that the mini-lozenge would be ——— the size of the original lozenge and would be marketed ——————— Due to the significant change in the size of the lozenge and the concerns about chemical equivalency, the FDA determined that the new mini-lozenge was a new formulation and that a new NDA was required. b(4)

At the January 9, 2008 meeting, the initial pharmacokinetic studies for the reformulated 2 mg and 4 mg lozenges were discussed. Concerns raised by the FDA included an apparent discrepancy in AUC and C_{max} between the original lozenge and the new proposed product and an additional study using a U.S. population was advised. There was also discussion regarding the dissolution time for the mini-lozenge and the safety with the increased oral concentration of the active ingredient. FDA was particularly concerned about local effects in the mouth and GSK agreed to provide more information on absorption and local safety. GSK was also given information regarding eCTD submission for the new NDA including the link to the 2006 *Guidance for Industry on eCTD Submissions.*

2.6 Other Relevant Background Information

There is no other relevant background information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

CMC review is pending.

3.2 Animal Pharmacology/Toxicology

Nicorette lozenges 2 mg and 4 mg are considered by the sponsor to be a line extension of the currently marketed Commit lozenges. They are available in the same strengths and contain the same active ingredient, nicotine polacrilex. Nicorette lozenges 2 mg and 4 mg provide plasma concentrations of nicotine that are not significantly different from the currently marketed Commit lozenges. In consideration of this fact, and given that substantial toxicological data on nicotine and its metabolites exist, referral is made to NDA 21-330 (Commit Lozenges) and its corresponding supplements for an in-depth review of toxicology data for nicotine that was previously published in the scientific literature.

Any additional pertinent pharmacology/toxicology data will be evaluated by the pharmacology/toxicology reviewers in DNCE.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Clinical data to support the proposed product come from:

- Three Phase II pharmacokinetic studies designed to demonstrate that the mini lozenge is bioequivalent to the previously marketed Commit® lozenge,
- Three Phase I pharmacokinetic studies submitted by the sponsor as part of the integrated summary of safety,
- NDA 21-330 Commit Nicotine Polacrilex Lozenges, 2 mg and 4 mg and approved supplements (002, 003, 004),
- IND 56,295 Nicotine Polacrilex Lozenges,
- Postmarketing Data including
    - GSK USA and Worldwide Adverse Event Database (all reports through data lock point 31 August, 2008)
    - FDA Adverse Event Reporting System database (all reports up to Quarter 1 of 2008)
    - World Health Organization International Drug Monitoring program (all reports through September, 2008)
    - Drug Abuse and Overdose Data from the Toxic Exposure Surveillance System, the American Association of Poison Control Centers (1997 to 2006) and the Drug Abuse Warning Network

- Literature Review regarding adverse events submitted by the sponsor (relevant articles since 1993) and
- Literature review submitted by the sponsor regarding ethnic differences in the metabolism of nicotine.

The Phase I pharmacokinetic studies were done using a different formulation of the mini lozenge. The active ingredient is the same (nicotine polacrilex) but the exact formulation is different from the proposed product. The information obtained from these studies is reviewed for adverse events, safety, and extent of exposure but is not included in the pharmacokinetics review.

4.2 Tables of Clinical Studies

Table 2: Tabular Listing of Phase I Clinical Studies

Study No [Reference]	Study Design*	Number of subjects	Treatments (dose in mg)	Duration of exposure	Sex
S2300319	Randomized, open, crossover, single dose	35	Nicotine Mini Mint 2 mg* Nicorette 2 mg Nicotine Mini Mint 4 mg* Nicorette 4 mg	Single dose; 20 subjects received the 2 mg dose and 15 received the 4 mg dose	24 M/11 F
S2300339	Randomized, open, crossover, multiple dose	44	Nicotine Mini Mint 1.5 mg Nicorette 2 mg	Multiple dose: 13 doses at one hourly intervals	30 M/ 14 F
S2300320	Randomized, open, crossover, single dose	30	Nicotine Mini Mint 4 mg Nicorette 4 mg	Single dose	21 M/ 9 F

* Two formulations of Nicotine Mini mint lozenge were investigated; one referred to as mannitol-based, and the other as mannitol master granulation (MMG).

Table 3: Tabular Listing of Phase II Clinical Studies

Study Number	Type of Study	Study Design	Number of Subjects	Study Objective
GSK S3010445	PK	Single Center, Open Label, Randomized, Single-Dose, 2-way crossover	28	Characterize the rate and extent of nicotine absorption of 2 mg mini lozenge to 2 mg Commit lozenge
GSK S3010466	PK	Single Center, Open Label, Randomized, Single-Dose, 2-way crossover	28	Characterize the rate and extent of nicotine absorption of 4 mg mini lozenge to 4 mg Commit lozenge
GSK S3010567	PK	Single Center, Open Label, Randomized, Single-Dose, 4-way crossover	40	Confirm the bioequivalence of 2 mg and 4 mg mini lozenges to standard 2 mg and 4 mg Commit lozenges

4.3 Review Strategy

This review covers safety data submitted from Phase I and Phase II studies to support the NDA. There are no new efficacy data. Pharmacokinetic data will be reviewed by the chemists. Any new toxicology data will be reviewed by the pharmacologist/toxicologist in the Division of Nonprescription Clinical Evaluation (DNCE).

4.4 Data Quality and Integrity

There were no discrepancies noted in the data or the analysis.

4.5 Compliance with Good Clinical Practices

The clinical studies included in the application were all conducted in accordance with Title 21, Parts 50 and 56 of the CFR. Informed consent was obtained from all subjects. All of the studies were conducted under the sponsorship of the applicant and were reviewed by Ethics Committees and Institutional Review Boards.

4.6 Financial Disclosures

The sponsor evaluated all clinical investigators involved in performing a study as part of this NDA and determined that none of the investigators had any financial interests in the product (as defined in 21 CFR 54.2) and that Form FDA 3455 was not applicable.

5 CLINICAL PHARMACOLOGY

Nicotine is a naturally occurring autonomic drug and an agonist at nicotine receptors in the peripheral and central nervous system. The pharmacology of nicotine is complex and includes a variety of autonomic effects, both adrenergic and cholinergic. The pharmacological effects of nicotine are generally dose-related. Low doses of nicotine cause ganglionic stimulation and high doses cause ganglionic blockade following brief stimulation.

For the purpose of this application, the pharmacology of nicotine can be sufficiently understood from the published literature. The primary pharmacodynamic action of nicotine in animal models is also considered to be superseded by the human data; thus, no additional nonclinical pharmacology studies are reported for mini lozenges 2 mg and 4 mg. For an overview of the major pharmacological actions of nicotine, referral is made to NDA 21-330 (Commit Lozenges) and its corresponding supplements.

5.1 Pharmacokinetics

Nicorette lozenges 2 mg and 4 mg completely dissolve in the oral cavity and the entire amount of nicotine contained in each lozenge becomes available for buccal absorption or ingestion. From the results of a single dose bioequivalence study, the mean peak plasma concentrations (C_{max}) of nicotine achieved from use of Nicorette Lozenges were 4.27 and 6.74 ng/ml for the 2 mg and 4 mg lozenges, respectively. In contrast, the maximum blood level of nicotine observed after smoking a cigarette is approximately 27 ng/ml while the steady state level of nicotine after repeated cigarette smoking averages 59.6 ng/ml.[1,2]
Review of the scientific literature by the sponsor revealed no recent publications regarding the absorption, distribution, or excretion of nicotine. Referral is made to NDA 21-330 (Commit Lozenges) and its corresponding supplements for an in-depth review of previously reported studies of the absorption, distribution, and excretion of nicotine.

Three separate Phase II clinical studies have been conducted to establish the biopharmaceutical characteristics of the Nicorette lozenge and to compare these with the marketed lozenge formulation, Commit. All studies were conducted using healthy volunteer smokers who were instructed not to smoke (or take other nicotine products) before and during the assessment period.

Study S3010445

This study assessed bioequivalence between the Nicorette 2 mg lozenge and the original Commit 2 mg nicotine lozenge. The design and methodology of the study was appropriate for establishing bioequivalence and complied with the relevant FDA guidelines. Table 4 summarizes the C_{max} and the AUC for the Nicorette 2 mg lozenge and shows equivalency to the Commit 2mg lozenge.

Table 4: Summary of S3010445 Baseline-Adjusted Nicotine Pharmacokinetic Variables

Parameter	Mean		Geometric Mean Ratio: Nicorette/Commit	
	Nicorette 2 mg	Commit 2 mg	Estimate	90% Confidence Interval
C_{max}(ng/ml)	7.10	6.51	104.66%	[96.70%, 113.27%]
$AUC_{(0-t)}$(ng*hr/mL)	29.02	28.77	98.55%	[88.57%, 109.66%]
T_{max} Median (hour)	0.92	1.00		

Study S3010466

This study assessed bioequivalence between the Nicorette 4 mg nicotine lozenge and the original Commit 4 mg nicotine lozenge. The design and methodology of the study was appropriate for establishing bioequivalence and complied with the relevant FDA guidelines. Table 5 summarizes the C_{max} and the AUC for the Nicorette 4 mg lozenge and shows equivalency to the Commit 4 mg lozenge.

Table 5: Summary of S3010466 Baseline-Adjusted Nicotine Pharmacokinetic Variables

Parameter	Mean		Geometric Mean Ratio: Nicorette/Commit	
	Nicorette 4 mg	Commit 4 mg	Estimate	90% Confidence Interval
C_{max}(ng/ml)	7.94	8.03	95.0%	[87.4%, 103.3%]
$AUC_{(0-t)}$(ng*hr/mL)	29.40	29.84	95.2%	[89.8%, 100.9%]
T_{max} Median (hour)	1.50	1.01		

Studies S3010445 and S3010466 were conducted to demonstrate bioequivalence of the new Nicorette formulation to the marketed formulation, Commit. Both these studies did in fact demonstrate the bioequivalence (per the applicant) of both the 2 mg and 4 mg Nicorette lozenges

to the respective doses of Commit. However, review of the pharmacokinetic parameters in these two studies did indicate some anomalies, specifically the C_{max} and $AUC_{(0-t)}$. In study S3010445, the C_{max} and $AUC_{(0-t)}$ for both the 2 mg Nicorette lozenge and the 2 mg Commit lozenge were higher than expected compared with the 4 mg doses (see Tables 4 and 5), although the T_{max} for both the 2 mg and 4 mg formulations was in line with expectations. For efficiency reasons these two studies were conducted in different geographic regions with different populations. Study S3010445 was conducted in India on an Indian population whereas study S3010466 was conducted in the United States on a U.S. population. Although it is often problematic to compare across studies, it is possible that there may be some population differences in nicotine absorption and/or elimination.[3,4,5,6] In addition, the Indian subjects in S3010445 had a lower average body mass index than the US subjects in S3010466 (22.0 vs. 23.9, respectively) and there are data to suggest, at least for transdermal nicotine formulations, body weight could have an influence on the pharmacokinetics of nicotine.[7] Consequently, an additional study was performed to confirm bioequivalence.

Study S3010567

This study assessed 1) the bioequivalence between the Nicorette 2 mg lozenge and the original Commit 2 mg lozenge and 2) the bioequivalence between the Nicorette 4 mg lozenge and the original Commit 4 mg lozenge. The design and methodology of the study was appropriate for establishing bioequivalence and complied with the relevant FDA guidelines. The standard criteria for establishing bioequivalence were used and predefined in the protocol. Table 6 summarizes Study S3010567 indicating bioequivalence to the Commit lozenge for both the 2 mg and 4 mg Nicorette lozenge in a United States population.

Table 6: Summary of S3010567 Baseline-Adjusted Nicotine Pharmacokinetic Variables

Parameter	Mean		Geometric Mean Ratio: Nicorette/Commit	
	Nicorette 2 mg	Commit 2 mg	Estimate	90% Confidence Interval
C_{max}(ng/ml)	4.27	4.49	95.12%	[90.0%, 100.53%]
$AUC_{(0-t)}$(ng*hr/mL)	11.94	12.35	94.12%	[87.78%, 100.92%]
T_{max} Median (hour)	0.86	0.84		
Parameter	Nicorette 4 mg	Commit 4 mg	Estimate	90% Confidence Interval
C_{max}(ng/ml)	6.74	7.71	88.39%	[82.85%, 94.32%]
$AUC_{(0-t)}$(ng*hr/mL)	22.71	25.41	91.32%	[85.29%, 97.78%]
T_{max} Median (hour)	1.00	1.00		

Reviewer Comments: The three pharmacokinetic studies show bioequivalence of the Nicorette lozenge with the previously approved Commit lozenge.

5.2 Pharmacodynamics

There are no pharmacodynamic data submitted with this NDA.

5.3 Exposure-Response Relationships

There are no data on exposure-response relationships submitted with this NDA.

6 INTEGRATED REVIEW OF EFFICACY

There are no new efficacy data in this NDA submission. The efficacy of the marketed lozenge formulation was established in the pivotal safety and efficacy study (S1410043) in the approved original NDA 21-330. Study S3010567 indicated bioequivalence to the marketed Commit lozenge for both the 2 mg and 4 mg product and further efficacy study was felt not to be needed.

6.1 Indication

The indication is identical to the currently approved Commit lozenges; "reduces withdrawal symptoms, including nicotine craving associated with quitting smoking."

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety data to support this NDA comes from:

- Adverse Event reports from the Phase I studies (S2300319, S2300339, and S2300320)
- Adverse Event reports from the Phase II studies (S3010445, S3010466, and S3010567)
- Post-marketing safety data including :
  - GSK USA and Worldwide Database (all reports through data lock point 31 August, 2008)
  - FDA Adverse Event Reporting System database (all reports up to Quarter 1 of 2008)
  - World Health Organization International Drug Monitoring Program (all reports through search in September, 2008)
  - American Association of Poison Control Centers database (1997 to 2006)
  - Drug Abuse Warning Network
- Review of the literature by the sponsor (relevant articles since 1993)

7.1.1 Deaths

There were no deaths during the Phase I or Phase II studies.

7.1.2 Other Serious Adverse Events

There were no serious adverse events during the Phase I or Phase II studies.

7.1.3 Dropouts and Other Significant Adverse Events

One subject dropped out of Study #S3010567 due to generalized papules and pruritis after receiving the 2 mg Commit lozenge. The rash resolved without treatment. It was thought that this was possibly related to the medication.

There were seven other subjects that dropped out of Study #3010567 and four subjects that dropped out of Study #S3010466. Study #S3010445 had no subjects that dropped out. None of the other dropouts were thought to be related to the study medication. The reasons for subject discontinuation are noted in Table 7.

The Phase I studies (S2300339, S2300320, and S2300319) had no subjects that dropped out due to adverse events.

There were no significant adverse events in any of the studies.

7.1.3.1 Overall profile of dropouts

Table 7: Summary of Subject Disposition in Pharmacokinetic Studies

Study #	Enroll	Complete	Reason for Discontinuation				
			Adverse Event	Withdrew Consent	Lost to Follow-up/ Noncompliant	Failed Drug Screen	Other/ Personal
S2300339	44	38		2	1	1	1
S2300320	30	25			2	1	2
S2300319 2 mg	20	17			1		2
S2300319 4 mg	15	12			1	1	1
S3010445	28	28					
S3010466	28	24		4			
S3010567	40	32	1	2	3	1	1 (dental extraction)

7.1.3.2 Other significant adverse events

There were no other significant adverse events in the pharmacokinetic studies.

7.1.4 Other Search Strategies

Not applicable

7.1.5 Common Adverse Events

Common side effects known to be associated with nicotine replacement products include:

- Nausea or upset stomach
- Watering eyes
- Dizziness
- Headache
- Hiccups or belching
- Tingling of mouth or lips (gum and lozenge)
- Sore throat
- Dry mouth
- Skin irritation (patch)

7.1.5.1 Eliciting adverse events data in the development program

During the Phase I and Phase II pharmacokinetic studies, at each visit after the initial screening visit, the subjects were questioned about any changes in their status or any symptoms that may have developed since their last visit. All adverse events were recorded and graded by the investigators for intensity and potential relationship to the medication.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events (including severity and relationship) were summarized by treatment. Adverse events were coded using the Medical Dictionary of Regulatory Activities (MedDRA). The coding of adverse events was appropriate.

7.1.5.3 Incidence of common adverse events

The incidence of adverse events was low. Most adverse events were mild in intensity. The Nicorette lozenge had an incidence similar to the Commit lozenge. The most common adverse events noted in the studies were nausea and gastrointestinal symptoms, headache, dizziness, and dry mouth and these events appeared to be dose related, i.e. occurring in greater frequency with the 4 mg dose than the 2 mg dose.

Of the 233 subjects enrolled in the Phase I studies, 134 received lozenges. Seventy-eight subjects received either the 1.5 mg or 2 mg lozenge and 56 received the 4 mg lozenge. There were 42 patients in study S2300339 that received thirteen doses of the 1.5 mg lozenge and 43% had an event possibly or probably related to treatment. The remaining subjects only received single doses of the treatments. Thirty-six subjects received a 2 mg lozenge and 6 (16.7%) experienced a treatment related adverse event. Fifty-six subjects received a 4 mg lozenge and 5

(9%) experienced a treatment related adverse event. The most common adverse events noted in the Phase I studies were gastrointestinal symptoms, dizziness, and headache. Most of the adverse events reported in the Phase I studies were in Study S2300339 when subjects received 13 doses of each of the study medications.

In the Phase II studies, 4.5% of subjects treated with 2 mg Nicorette lozenge, 6.3% of subjects treated with the 2 mg Commit lozenge, 24.1% of subjects treated with the 4 mg Nicorette lozenge, and 14.8% of subjects treated with the 4 mg Commit lozenge reported at least one treatment related AE. The most commonly reported treatment related adverse events (reported by >2 subjects) in the 4 mg Nicorette lozenge group were dizziness (3 subjects, 5.2%), headache (4 subjects, 6.9%), and nausea (6 subjects, 10.3%). In the 4 mg Commit lozenge group, the most commonly reported adverse event was nausea (3 subjects, 4.9%). No adverse events were reported by more than 2 subjects in the 2 mg Nicorette lozenge or 2 mg Commit lozenge groups.

7.1.5.4 Common adverse event tables

Tables 8, 9, and 10 summarize the adverse events from the Phase I studies (S2300339, S2300320, and S2300319). Table 11 summarizes the adverse events from the pooled Phase II studies (S3010445, S3010466, and S3010567).

Table 8: Incidence of Treatment Related Adverse Events in Study S2300319 (Phase I)

	2mg			4mg		
Adverse Event	Mini lozenge * (n=19) n (%)	Mini lozenge ** (n=17) n (%)	Gum (n=19) n (%)	Mini lozenge * (n=14) n (%)	Mini lozenge ** (n=13) n (%)	Gum (n=13) n (%)
Any Adverse Event	4 (21%)	2 (12%)	2 (11%)	2 (14%)	2 (15%)	1 (8%)
Eye Disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Eye irritation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Eye redness	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gastrointestinal Disorders	3 (16%)	0 (0%)	1 (5%)	1 (7%)	2 (15%)	1 (8%)
Dyspepsia	1 (5%)	0 (0%)	0 (0%)	1 (7%)	1 (8%)	1 (8%)
Nausea	2 (11%)	0 (0%)	1 (5%)	0 (0%)	1 (8%)	0 (0%)
Nervous System Disorders	2 (11%)	2 (12%)	1 (5%)	1 (7%)	0 (0%)	0 (0%)
Dizziness	1 (5%)	1 (6%)	0 (0%)	1 (7%)	0 (0%)	0 (0%)
Headache	1 (5%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)
Hypoaesthesia	0 (0%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Respiratory, thoracic, and mediastinal disorders	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Sneezing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Throat irritation	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Vascular disorders	0 (0%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Peripheral coldness	0 (0%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: S2300319 CSR, Table 9.3.1.4.1 and Table 9.3.1.4.2

* mannitol-based mini lozenge

** MMG-based mini lozenge

Reviewer Comments: This study used two different formulations for the nicotine polacrilex lozenges compared with the marketed nicotine polacrilex gum. Each subject received a single dose. A total of 36 patients received a 2 mg lozenge. Six (16.7%) had an adverse event. Twenty-seven patients received a 4 mg lozenge and four (14.8%) had an adverse event. In both groups, nausea was the most common AE. Other adverse events included headache, dizziness, and dyspepsia. There were no unexpected or unlabeled adverse events.

Table 9: Incidence of Treatment Related Adverse Events in Phase I Study S2300339

Adverse Event	1.5mg Mini lozenge (n=42) n (%)	2mg gum (n=41) n (%)
Any Adverse Event	**18 (43%)**	**10 (24%)**
Ear and labyrinth Disorders	**2 (5%)**	**0 (0%)**
Tinnitus	2 (5%)	0 (0%)
Gastrointestinal Disorders	**8 (19%)**	**5 (12%)**
Abdominal distension	1 (2%)	0 (0%)
Abdominal pain	0 (0%)	1 (2%)
Abdominal pain upper	2 (5%)	0 (0%)
Dyspepsia	1 (2%)	1 (2%)
Flatulence	1 (2%)	0 (0%)
Gastrooesophageal reflux disease	1 (2%)	0 (0%)
Gingival bleeding	0 (0%)	1 (2%)
Gingivitis	0 (0%)	1 (2%)
Nausea	4 (10%)	2 (5%)
Stomach discomfort	0 (0%)	1 (2%)
General disorders and administration site conditions	**2 (5%)**	**1 (2%)**
Feeling hot	0 (0%)	1 (2%)
Sensation of foreign body	2 (5%)	0 (0%)
Investigations	**1 (2%)**	**0 (0%)**
Heart rate increased	1 (2%)	0 (0%)
Nervous System Disorders	**10 (24%)**	**3 (7%)**
Dizziness	5 (12%)	1 (2%)
Headache	5 (12%)	3 (7%)
Respiratory, thoracic, and mediastinal disorders	**8 (19%)**	**4 (10%)**
Dyspnoea	0 (0%)	1 (2%)
Hiccups	5 (12%)	1 (2%)
Pharyngolaryngeal pain	0 (0%)	2 (5%)
Throat irritation	3 (7%)	0 (0%)
Skin and subcutaneous tissue disorders	**1 (2%)**	**0 (0%)**
Hyperhidrosis	1 (2%)	0 (0%)
Vascular disorders	**1 (2%)**	**0 (0%)**
Pallor	1 (2%)	0 (0%)

Source: S2300339 CSR, Table 9.3.1.4

Reviewer Comments: This study compared the 1.5 mg nicotine polacrilex lozenge to the 2 mg gum. Each subject received 13 doses of the treatments. Forty-two patients received the lozenge and 18 (43%) had at least one possible or probable treatment related adverse event. The most common adverse events were nausea, dizziness, headache, hiccups, and throat irritation. None of the adverse events were unexpected or unlabeled.

Table 10: Treatment Related Adverse Events in Phase I Study S2300320

Adverse Event	4mg Mini lozenge (n=29) n (%)	2mg gum (n=26) n (%)
Any Adverse Event	1 (3%)	1 (4%)
Nervous System Disorders	1 (3%)	1 (4%)
Dizziness	1 (3%)	1 (4%)

Source: S2300320 Table 9.3.1.4

Reviewer Comments: This study compared a single dose of the 4 mg lozenge to the 4 mg gum. (The sponsor's table is labeled incorrectly.) There was only one reported treatment related adverse event reported for the lozenge – dizziness. There were no unexpected adverse events.

Table 11: Treatment Related Adverse Events, Pooled Phase II Studies

MedDRA preferred term	Mini 2mg (n=60) n (%)	Standard 2mg (n=63) n (%)	Mini 4mg (n=58) n (%)	Standard 4mg (n=61) n (%)
Any Adverse Event	**3 (4.5%)**	**4 (6.3%)**	**14 (24.1%)**	**9 (14.8%)**
Gastrointestinal Disorders	**1 (1.5%)**	**0 (0%)**	**9 (15.5%)**	**5 (8.2%)**
Nausea	0 (0%)	0 (0%)	6 (10.3%)	3 (4.9%)
Dyspepsia	0 (0%)	0 (0%)	1 (1.7%)	0 (0%)
Stomach discomfort	0 (0%)	0 (0%)	2 (3.4%)	0 (0%)
Abdominal rigidity	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)
Dry mouth	0 (0%)	0 (0%)	0 (0%)	1 (1.6%)
Tongue eruption	0 (0%)	0 (0%)	0 (0%)	1 (1.6%)
Nervous System Disorders	**2 (3.0%)**	**2 (3.2%)**	**6 (10.3%)**	**5 (8.2%)**
Headache	0 (0%)	0 (0%)	4 (6.9%)	2 (3.3%)
Dizziness	1 (1.5%)	2 (3.2%)	3 (5.2%)	2 (3.3%)
Dysgeusia	1 (1.5%)	0 (0%)	0 (0%)	1 (1.6%)
Respiratory, Thoracic and Mediastinal Disorders	**1 (1.5%)**	**0 (0%)**	**2 (3.4%)**	**0 (0%)**
Hiccups	1 (1.5%)	0 (0%)	1 (1.7%)	0 (0%)
Pharyngolaryngeal pain	0 (0%)	0 (0%)	1 (1.7%)	0 (0%)
General Disorders and Administration Site Conditions	**0 (0%)**	**1 (1.6%)**	**0 (0%)**	**1 (1.6%)**
Asthenia	0 (0%)	0 (0%)	0 (0%)	1 (1.6%)
Chest pain	0 (0%)	1 (1.6%)	0 (0%)	0 (0%)
Skin and Subcutaneous Disorders	**0 (0%)**	**1 (1.6%)**	**1 (1.7%)**	**0 (0%)**
Hyperhidrosis	0 (0%)	0 (0%)	1 (1.7%)	0 (0%)
Pruritus generalized	0 (0%)	1 (1.6%)	0 (0%)	0 (0%)
Rash papular	0 (0%)	1 (1.6%)	0 (0%)	0 (0%)
Ear and Labyrinth Disorders	**0 (0%)**	**0 (0%)**	**1 (1.7%)**	**0 (0%)**
Tinnitus	0 (0%)	0 (0%)	1 (1.7%)	0 (0%)
Psychiatric Disorders	**0 (0%)**	**0 (0%)**	**0 (0%)**	**1 (1.6%)**
Nervousness	0 (0%)	0 (0%)	0 (0%)	1 (1.6%)

Source: ISS Table 9.3.3

Reviewer Comments: All of the Phase II studies were single dose, pharmacokinetic studies. There were no unexpected or unlabeled adverse events reported.

7.1.5.5 Identifying common and drug-related adverse events

A total of 30 adverse events possibly or probably related to treatment were reported in the Phase II trials (see Table 11). Most of these were mild in intensity. None of the adverse events were serious. The Phase I studies were conducted with two different formulations (mannitol-based

and MMG-based) and in a different dose from the submitted products. All of the adverse events were mild. The most commonly reported events included nausea, dizziness, headache, and hiccups. This pattern was similar to the Phase II trials and to the previously described adverse events from nicotine polacrilex lozenges. There were more adverse events noted in the multi-dose study (S2300339) and in subjects that received the 4 mg dose.

7.1.5.6 Additional analyses and explorations

There were no additional analyses or explorations performed by the sponsor.

7.1.6 Less Common Adverse Events

The number of subjects and adverse events was too small to accurately assess the incidence of less common adverse events.

7.1.7 Laboratory Findings

During the Phase II studies, laboratory testing was performed prior to drug administration as part of the patient screening process. This included:

- Hematology - Hemoglobin, white blood cells (WBC) with differentials, and platelet
- Biochemistry – ALT, AST, alkaline phosphatase, creatinine, BUN, bilirubin, glucose
- Virology – Hepatitis B, Hepatitis C, and HIV screening
- Urinalysis - dipstick for glucose only

Serum pregnancy tests were done on all female subjects before each dose was given. Expired carbon monoxide (CO) measurements were obtained immediately before dose administration and immediately after the last PK sample was collected. Random CO measurements were collected during the study (at least four measurements from each subject).

A urine sample was analyzed for each subject for cannabinoids, amphetamine, cocaine, ecstasy, methamphetamine, opiates, and alcohol before each dose of nicotine polacrilex was given.

There was no laboratory testing done at the end of the study. In Protocol S301567, the hemoglobin level was re-checked during the baseline of each study session and did not significantly change.

Comments: The results of all abnormal screening laboratory tests were reviewed. Most of these abnormalities were not clinically significant. There were patients excluded from the studies due to more significant abnormalities (anemia, hepatitis C, and elevated liver function tests) and for positive drug or alcohol screens. None of the abnormalities were related to the study medication.

7.1.8 Vital Signs

Vital signs were checked on all patients prior to drug administration in each study. The vital signs fell into a normal range and were not rechecked after medication was given. There were patients that initially had elevation of systolic or diastolic blood pressure. These were rechecked and had normalized. There were no dropouts or outliers identified due to abnormal vital signs.

7.1.9 Electrocardiograms (ECGs)

ECG testing was done as part of the patient screening for each study. There were no clinically significant abnormalities. A total of 96 patients were tested, 15 had minor ECG changes, and none were withdrawn from a study. There were no ECGs done after medication administration.

7.1.10 Immunogenicity

Immunogenicity was not assessed.

7.1.11 Human Carcinogenicity

There was no data on human carcinogenicity submitted with this application.

7.1.12 Special Safety Studies

The Nicorette lozenge is smaller in size than the currently marketed Commit lozenge and dissolves in the mouth is approximately half the time. In the pivotal study S3010567 the *in vivo* dissolution for the Nicorette lozenge was about 12 minutes (12.5 min for 2 mg and 11.2 min for 4 mg) compared to 25 minutes for Commit (25.0 min for 2 mg and 25.6 min for 4 mg). At a meeting with the FDA on 1/29/08 a concern was raised that the more rapid dissolution of the Nicorette lozenge may result in a higher oral cavity nicotine level and possibly increased side effects. FDA requested that the sponsor address this issue.

The sponsor responds that the Nicorette lozenge, as with the Commit lozenge, is intended to be moved around the mouth until completely dissolved. This is different from the nicotine gum and the sublingual tablets which are placed in one location for some or all of the time they are being used. GSK believes that the movement around the mouth will disperse the nicotine and decrease the likelihood of an area of increased local concentration. If such an increase did have an impact on the tolerability of the new product this would likely be seen as reports of adverse events related to the mouth or throat or possibly the gastrointestinal tract (if swallowing of nicotine was an issue). Review of adverse events from Studies S3010567, S3010445, and S3010466 (see Table 11 above) show relatively few incidences of problems related to the mouth or throat. There is one report of pharyngolaryngeal pain for both the 4 mg Nicorette lozenge and 4 mg Commit and one report of tongue eruption for 4 mg Commit. Of events possibly related to swallowing of nicotine there was one report of hiccups for both the 2 mg and 4 mg Nicorette lozenge but none for either dose of Commit. Only for nausea was there an apparent difference between the Nicorette lozenge and Commit; with 7 reports (about 12% of subjects) for 4 mg

Nicorette lozenges and 3 reports (about 5% of subjects) for Commit. All but one of these reports of nausea were rated as mild in intensity, with the remaining one being rated as moderate.

The sponsor believes that taken together this slight increase in reports of hiccups and nausea may suggest a slight increase in the proportion of nicotine swallowed for the Nicorette lozenge compared to Commit. However, this difference is unlikely to be major as the products are bioequivalent; if a significant proportion of the nicotine was being absorbed via a different route (i.e. through the gut rather than buccally) a difference in pharmacokinetic profile would have been seen between the two formulations. Both nausea and hiccups are included as potential adverse effects in the proposed labeling for the Nicorette lozenge. No new adverse events unique to the Nicorette lozenge formulation were identified.

Reviewer Comments: There was no increase in adverse events that would be related to oral irritation. The Nicorette lozenge is bioequivalent to the Commit lozenge. The faster dissolution time does not seem to be of clinical concern.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Nicotine replacement products are indicated for reduction of withdrawal symptoms and cravings in patients that are trying to quit smoking. The principal addicting substance in cigarettes is nicotine and the replacement products are preferable to cigarettes since patients are not exposed to the other, more harmful, cigarette ingredients.[8] The long-term effects of cigarette use are well defined and known to be dangerous. Nicotine replacement products have the potential to be addicting due to the nicotine, but the use of NRT products is believed to be safer than continued cigarette use (though the data is limited in pregnant women and children).[9] Gradual withdrawal of nicotine using the replacement products increases the likelihood of smoking cessation and these medications are not thought to have significant abuse potential.

As part of the safety review, FDA requested GSK to evaluate the potential for misuse or abuse of nicotine polacrilex (gum or lozenge) in all populations. Table 12 summarizes the GSK USA and Worldwide Database of all reports through a data lock point of 31 August, 2008. There were thousands of reported events but few (< 5%) were serious and even fewer that were medically verified. Of more concern is the number of patients that report using the products far longer than the recommended treatment time.

Table 12: Summary of Use, Extended Length of Use, and Serious Events for Gum and Lozenge in All Populations from GSK Database

	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge
Events Reported	19,202	11,181
Serious Events Reported	837 (4.4%)	375 (3.3%)
Medically Verified and Serious	173 (0.9%)	10 (<0.1%)
Total Episodes of Use	19335	11243
Duration of Use Known	7628 (39.4%)	5391 (47.9%)
Use ≤ 6 months	6361 (83.4%)	4895 (90.8%)
Use 6 months – 1 year	217 (2.8%)	114 (2.1%)
Use 1year – 2 years	221 (2.9%)	168 (3.1%)
Use > 2 years	829 (10.9%)	214 (4.0%)

The AERS database was searched from time of initial marketing up to Quarter 1 of 2008 for *drug abuse, intentional misuse, overdose, and dependence* terms for Nicorette® and Commit®. Table 13 shows that about 10% of the total events reported were serious events but details were lacking.

Table 13: Summary of Abuse, Misuse, Overdose, and Serious Events for Gum and Lozenge in All Populations from AERS Database

	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge
Total Events Reported	9409	3274
Total Serious Events	1183 (12.6%)	279 (8.5%)
Total Abuse, Misuse, Overdose or Dependence	3376 (35.9%)	732 (22.4%)

The WHO database was searched for *drug dependence and/or drug abuse* in the data set with Nicorette® and Commit® through September, 2008. Table 14 summarizes the results. The number of reported events is small but serious events are more common with the lozenge.

Table 14: Summary of Abuse, Misuse, Overdose, and Serious Events for Gum and Lozenge in All Populations from WHO Database

	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge
Total Events Reported	982	637
Total Serious Events	29 (2.9%)	83 (13.0%)
Total Abuse, Misuse, Overdose	415 (42.3%)	76 (11.9%)

The AAPCC data from 1997 through 2006 showed a total of 8098 exposures to a nicotine pharmaceutical agent. The formulation (patch, gum, or lozenge), dose, and duration are not known. There were 5401 cases of "unintentional exposure" and 783 cases of "intentional

exposure." Table 15 summarizes the demographic profile of the exposure cases listed with AAPCC.

Table 15: Exposure Cases of Nicotine Pharmaceuticals from 1997 to 2006 from AAPCC Database

		Age in Years			Reason				Outcome			
Year	Numb of Exp[1]	<6	6- 19	>19	Unint.[2]	Int.[3]	Other	Ad. Reac.[4]	None or Minor	Mod[5]	Major	Death
1997	856	189	73	545	460	99	1	294	357	74	2	0
1998	725	189	81	415	423	73	1	225	297	55	0	0
1999	750	221	80	409	481	77	2	189	303	55	0	1
2000	743	257	77	402	483	72	3	183	316	56	3	0
2001	676	258	75	339	472	66	0	135	265	45	6	2
2002	808	320	79	404	557	72	1	176	322	53	1	0
2003	725	260	75	382	482	81	2	155	281	41	0	1
2004	867	358	84	420	618	79	2	160	370	48	3	1
2005	1024	437	91	493	727	109	3	178	437	51	1	0
2006	924	446	80	344	698	55	0	169	409	45	1	0
Total	**8098**	**2935**	**795**	**4176**	**5401**	**783**	**15**	**1864**	**3357**	**523**	**17**	**5**

1: Number of Exposures; 2: Unintentional Exposure; 3: Intentional Exposure; 4: Adverse Reactions; 5: Moderate

Reviewer Comments: In spite of the package labeling, it is clear that some patients use nicotine replacement products far longer than the recommended time period. Based on the data from GSK, AERS, and WHO, prolonged use, misuse, and abuse appear to be more of a problem with the nicotine gum than with the lozenge. The gum has been marketed for a longer period and this may also be reflected in these numbers. The incidence of serious events is variable among the three databases and this is likely due to duplicate cases and differences in reporting standards. The marked variability makes interpretation of these data difficult.

7.1.14 Human Reproduction and Pregnancy Data

Data on the use of nicotine replacement products in pregnancy and the effects on infants are limited. Studies in pregnant women have shown that while there is a risk with NRT products, smoking has an even greater risk due to the toxins in the cigarette smoke.[10] As part of the safety review, FDA requested GSK to provide data regarding the use and the potential for abuse or risk to mother or infant with the use of NRT (gum or lozenge) in pregnant or nursing women. Table 16 summarizes the case reports from the GSK USA and Worldwide Database (all reports through a data lock point 31 August 2008). The most common outcome after exposure is a normal infant with no apparent abnormality or outcome unknown. In the cases of documented abnormalities, there were none that were clearly associated with the NRT product exposure.

Table 16: Summary of Case Reports involving Pregnant Women for GSK Database

	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge
Live Infant, no apparent congenital abnormality	8	6
Spontaneous Abortion, no apparent abnormality	3[a]	0
Live Infant with congenital abnormality	3[b]	1[c]
Stillbirth, no apparent congenital abnormality	0	1[d]
Pregnancy Ongoing	1	0
Lost to Follow-Up	2	0
Unknown	20	10
TOTAL	**37**	**18**

[a] None of these cases were medically verified, there was not enough detail to assess if caused by nicotine
[b] 1. Mother used nicotine gum for 9 days while also smoking, baby born at 25 wks with unspecified defect
2. Baby born with malformed foot and cleft palate – questionable related to gum use by mom when pregnant
3. Mother smoked, then had PROM at 24 weeks, given gum in hosp, continued to smoke and use gum, baby born at 27 weeks, diagnosed with CP at 6 months, also had seizures and multiple handicaps
[c] Abortion occurred 3 days after using lozenge at a party where others were smoking cigars
[d] Mom used lozenges for 2 weeks in 1st trimester; then had intrauterine death – thought by physician to be unrelated

Table 17 summarizes the reports from the FDA Adverse Event Reporting System related to Nicorette gum up to the end of Quarter 1, 2008. Table 18 summarizes the reported cases to AERS for Commit lozenge for the same reporting period. The number of reported exposures to both products is small and there is not a clear association between exposure and effects on the pregnancy or infant.

Table 17: Summary of Cases related to Pregnancy and Nicorette from AERS Database

MedDRA Preferred Term	Number of Cases	MedDRA Preferred Term	Number of Cases
Abnormal labour	1	Death neonatal	1
Abortion	2	Drug exposure during pregnancy	28
Abortion spontaneous	5	Drug exposure via breast milk	2
Antepartum haemorrhage	1	Foetal arrhythmia	1
Bradycardia foetal	2	Foetal disorder	3
Breech delivery	1	Foetal growth retardation	1
Cerebral palsy	1	Galactostasis	1
Complications of pregnancy	1	Pre-eclampsia	2
Intra-uterine death	3	Precipitate labour	1
Intrauterine infection	1	Pregnancy	2
Labour complication	1	Premature baby	3
Lactation disorder	1	Premature labour	2
Maternal drugs affecting foetus	8	Premature separation of placenta	1
Neonatal disorder	2	Prolonged labour	1
Neonatal respiratory distress syndrome	1	Small for dates baby	2
Oligohydramnios	1	Stillbirth	3
Placental disorder	2	Umbilical cord abnormality	1
Placental Insufficiency	2	Umbilical cord around neck	1
Umbilical cord short	1	Unintended pregnancy	2
TOTAL	**96**		

Table 18: Summary of Cases related to Pregnancy and Commit form AERS Database

MedDRA Preferred Term	Number of Cases
Abortion spontaneous	1
Death neonatal	1
Drug exposure during pregnancy	4
Premature labour	1
TOTAL	7

The sponsor found no specific information regarding nicotine replacement products and use in pregnant women in the WHO and AAPCC databases.

Reviewer Comments: Nicotine products should not be used while pregnant or nursing. The product label advises pregnant or nursing women to only use nicotine replacement products on the advice of their health care provider. Based on the submitted safety data reports, there is no need to change current labeling.

7.1.15 Assessment of Effect on Growth

No assessment of the effects on growth done as part of this application.

7.1.16 Overdose Experience

There were no new data regarding overdose experience with this application. The GSK database was searched using MedDRA preferred terms for abuse/misuse, overdose, and dependence (all reports with a data lock point of 31 August 2008). A summary of these results is presented in Table 19.

Table 19: Number of events in GSK Database reported using MedDRA terms for Abuse, Misuse, and Overdose of Nicotine Polacrilex gum and lozenge

SOC - MedDRA preferred terms	Gum N*	Lozenge N*
Abuse and intentional misuse		
Drug Abuse	536	370
Intentional drug misuse	2113	1129
Overdose		
Intentional overdose	3	0
Overdose	92	25
Nicotine poisoning	7	0
Accidental overdose	5	0
Dependence		
Dependence	353	63
Drug dependence	2092	17
Nicotine dependence	652	537
Total number of events	5853	2171
Total number of cases N (% of all reports)	**5117 (26.6%)**	**1805 (16.1%)**

** N = number of events (except last row), a case could have had more than one event.*

Comments: Although the number of reports seems high, these results also include cases where NRT was used beyond the recommended duration of treatment.

7.1.17 Postmarketing Experience

At the request of FDA, an integrated safety review was submitted. This review focused on postmarketing data. These will be summarized by database, recognizing that many of the described cases may be recorded in more than one database.

A. GSK USA and Worldwide Adverse Event Database

All spontaneous reports that listed nicotine polacrilex as a suspect drug were included up to 31 August 2008. The results are summarized in Table 20. The total number of adverse events reported for the gum was 19,202; for the lozenge 11,181. At FDA request, a search was done specifically looking for evidence of misuse or abuse by children under age 18. These results are presented in Table 21. Most cases of exposure to nicotine polacrilex by children under age 12 were accidental.

For all age groups, the most common adverse events for both the gum and the lozenge were gastrointestinal. Other common adverse events were related to psychiatric issues, general disorders, and respiratory and thoracic disorders. This pattern is consistent with the adverse events noted in the Phase I and Phase II trials for the Nicorette lozenge.

Table 20: Percentage of Primary Adverse Events by Organ Class for Nicotine Polacrilex Gum and Lozenge from GSK Database

	GI disorder	Psychiatric	Respiratory Thoracic & Mediastinal	General disorder &Admin site	Nervous System	Skin	Injury or Poisoning	Musculo-skeletal	Cardiac
Gum	36.1	17.4	9.8	8.8	6.9	4.1	8.1	1.4	1.3
Lozenge	43.7	7.2	16.9	8.6	6.3	2.6	7.7	0.6	0.9

Table 21: Summary of Case Reports in Children < 18 from GSK Worldwide Database

	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge
Age < 12	Total:13 4-Intentional Drug Misuse 4-Accidental Overdose 2-Serious (1 Acc OD in 20mo old – resolved & 1 in-utero exposure – baby born at 25 wks – mom smoked and used gum – baby had multiple birth defects[a]	Total: 12 8-Accidental Exposure 2-Drug Administration Error 1-Serious – 16mo chewed ½ lozenge, treated with charcoal; recovered
Age 12-17	Total: 37 Most Common – Nausea, Vomiting, Abdominal Pain 1-Serious (16yo took 20 pieces of 4mg in 17 hrs-passed out & hit head) 2-Intentional Misuse 1-Intentional Misuse/OD (case above) 1-Administration Error/OD 1-Nicotine Dependence	Total: 9 Most Common – Nausea, Vomiting, Abdominal Pain, Throat Irritation 1-Intentional Misuse 1-Accidental Exposure 1-Intentional Misuse & Nicotine Dependence

[a] It is unclear that the defects are related to exposure to the gum

The GSK Database was also reviewed regarding abuse potential or overdose experience for the nicotine gum or lozenge. These results were reviewed in section 7.1.13 (Table 12) and section 7.1.16 (Table 19). The GSK Database was queried regarding use or abuse of nicotine replacement therapy by pregnant or nursing women. These results were included in section 7.1.14 (Table 16).

Comments: Misuse or abuse by those under age 18 is not a frequently reported event.

B. AERS Database

This database was searched for all reports for Nicorette and Commit up to quarter 1 of 2008. The summary by organ system and primary event is presented in Table 22. The total number of reports for the gum was 9409; for the lozenge 3274. The most commonly reported adverse events were gastrointestinal, psychiatric, and general disorders.

At FDA request, a search was done specifically looking for evidence of misuse or abuse by children under age 18. These results are presented in Table 23. The number of reported cases is very small and more commonly reported with the gum. This could be related to a longer marketing history.

Table 22: Percentage of Primary Adverse Events by Organ Class for Nicotine Polacrilex Gum and Lozenge from AERS database through Quarter 1, 2008

	GI Disorder	Psychiatric	General	Nervous System	Injury or Poisoning	Respiratory	Skin	SocCi	Cardiac
Gum	27.2	15.8	12.5	9.0	8.9	3.9	3.9	3.2	2.1
Lozenge	32.9	7.7	13.9	6.6	10.9	12.7	2.5	3.5	1.0

SocCi: Social Circumstances

Table 23: Summary of Case Reports in Children under age 18 from AERS Database

	Nicotine Polacrilex Gum	Nicotine Polacrilex Lozenge
Age < 18	Total: 45 8-Abuse/Dependence/Overdose	Total: 8 2-Abuse/Dependence/Overdose

The AERS database was also reviewed regarding abuse potential or overdose experience for the nicotine gum or lozenge. These results were reviewed in section 7.1.13 (Table 13). In addition, the AERS Database was queried regarding use or abuse of nicotine replacement therapy by pregnant or nursing women. These results were included in section 7.1.14 (Tables 17 and 18).

C. WHO Database

A search of this database was done by the sponsor (all reports through September, 2008)) and the adverse events are reported by organ system for the gum and the lozenge. The data is summarized in Table 24. The total number of reports for the gum was 982; for the lozenge 637. Similar to the other databases, gastrointestinal and psychiatric events were the most common.

Table 24: Percentage of Primary Adverse Events by Organ Class for Nicotine Polacrilex Gum and Lozenge from WHO Database

	Psychiatric	GI Disorder	General	Nervous System	Skin	Respiratory	Cardiac	SocCi	Infection
Gum	44.4	27.9	12.2	11.6	6.6	4.6	4.7	0.5	3.2
Lozenge	14.9	51.5	44.4	14.4	5.3	18.4	4.2	9.9	10.2

SocCi: Social Circumstances

Age was not reported consistently in this database so data for misuse or abuse by children under age 18 was limited. The median reported age in reported cases for the gum was 46.5 years and for the lozenge was 54 years. There were no cases of "drug dependence and/or drug abuse" reported by individuals under age 18 (when age was reported).

The WHO database was also reviewed regarding abuse potential or overdose experience for the nicotine gum or lozenge. These results were reviewed in section 7.1.13 (Table 14). In addition, the WHO Database was queried regarding use or abuse of nicotine replacement therapy by pregnant or nursing women. No information was received as a result of this search.

D. Drug Abuse and Overdose Data from the Toxic Exposure Surveillance System American Association of Poison Control Centers, Drug Abuse Warning Network

The Drug Abuse and Overdose Data from the Toxic Exposure Surveillance System, the American Association of Poison Control Centers (1997 to 2006) and the Drug Abuse Warning Network databases were searched by the sponsor. The Drug Abuse Warning Network had no responses (per the sponsor) related to nicotine replacement therapy products (gum or lozenge). The 2006 data from AAPCC showed a total of 924 exposures to a nicotine pharmaceutical agent. The formulation (patch, gum, or lozenge), dose, and duration are not known. There were 698 cases of "unintentional exposure" and 55 cases of "intentional exposure." There were no deaths.

This database has limited information regarding age, so the misuse or abuse by children under age 18 is difficult to asses. The most recent year for which data is available is 2006. Of the 924 reported cases of exposure, 446 cases were under age 6 and 80 were ages 6 to <19. A total of 698 cases were "unintentional" exposure, but it is unknown how many of these were in children. There was 1 case listed as "major," 45 as "moderate," and 150 "minor." There were no deaths.

Comments: The review of postmarketing adverse event data shows that nicotine polacrilex is generally well tolerated in both the gum and the lozenge forms. The lozenge is more likely to be associated with gastrointestinal disorders. The pattern of adverse events is consistent with the current package labeling. Other common adverse events include respiratory problems (including hiccups), psychiatric symptoms, and "general disorders." There were no studies or reports that had any unexpected adverse events or safety findings. The product label currently warns patients to avoid use in pregnancy or when nursing and not to use other nicotine containing products while using nicotine replacement therapy. Patients are also advised to discuss use with a physician if they have a cardiac history, hypertension that is uncontrolled, stomach ulcers or diabetes. The postmarketing experience would not indicate a need to include additional warnings on the product label.

GSK also provided a safety update at the end of October, 2008. These will be summarized by database, recognizing that many of the described cases may be recorded in more than one database.

A. GSK Worldwide Adverse Event Database

The GSK Worldwide Adverse Event Database was searched on 29 October 2008 using the following criteria:

- Data lock: 01 September 2008 to 28 October 2008
- Report types: All spontaneous reports, post-marketing surveillance reports, and unblinded serious clinical trial reports (attributable and non-attributable) where nicotine polacrilex lozenge formulation was reported as a suspect drug

A total of 122 reports were identified. None of these reports concerned children or adolescents under age 18 and there were no reports of use during pregnancy. There were

50 reports categorized as potential cases of Overdose or Drug Abuse; most of these were intentional abuse and involved use beyond the labeled duration. As shown in the Table 25, very few of the reports were serious or medically verified and most reports originated in the United States.

Table 25: GSK Adverse Event Data Sept and Oct 2008

Reports	Number (% of Total)
Total	122
Serious	7 (5.7%)
Medically Verified by Health Care Provider	1 (0.8%)
Medically Verified by Health Care Provider and Serious	0
US Reports	95 (77.9%)

B. AERS

A listing of all reports for Commit Lozenge added to FDA Adverse Event Reporting System (AERS) during 2nd Quarter 2008 was included. There were previously a total of 3274 cumulative reports (up until end of 1st Quarter 2008). A total of 2 reports were added during 2nd Quarter. One report involved intentional drug misuse in a 63 year old patient. The other report was for symptoms not likely attributable to Commit.

C. World Health Organization

Data was submitted from World Health Organization for the 3rd Quarter of 2008 for Adverse Events involving Commit Lozenges. There were a total of 832 reports which was disproportionately large compared to a total of 637 reports cumulatively up to 2nd Quarter 2008. GSK investigated and states that the discrepancy was attributable to the uploading of an annual US Periodic Report by WHO during this period. All of the cases were from the United States.

The pattern of reporting was similar to the previously submitted cumulative data. The most common events were Gastrointestinal Disorders (27%, 442 of 1660 events), followed by General Disorders (26%, 425 of 1660 events). There were also 341 of 1660 events reported as Social Circumstances related to the MedDRA Preferred Term "Drug Abuser" (21%). A detailed analysis of this report is not available due to the summary structure but none of the cases where age was specified concerned children or adolescents under age 18. Table 26 summarizes the WHO data.

Table 26: WHO Adverse Event Data Sept and Oct 2008

Reports	Number (% of Total)
Total	832
Serious	112 (13.5%)
Medically Verified by Health Care Provider	7 (0.8%)
United States Reports	832 (100%)

D. TESS, AAPCC, and DAWN

There was no update from the Toxic Exposure Surveillance System (TESS) from the American Association of Poison Control Centers (AAPCC). There are no data regarding nicotine from the Drug Abuse Warning Network (DAWN). GSK also reports that the company monitors published literature on a monthly basis and no new published safety information has been identified since the original post-marketing review was submitted.

GSK concludes that the 120 day update shows no material change from the cumulative analysis previously submitted.

Reviewer Comments: The updated safety report shows no significant change in information. This report only included the Commit lozenge and reported events are consistent with current package labeling.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

There are six studies submitted with this NDA. The three phase I studies are reviewed for safety and patient exposure. The three phase II studies are reviewed for pharmacokinetics as well as safety and patient exposure. There has been extensive exposure to nicotine polacrilex since it was first marketed. This exposure is reflected in the integrated safety summary and is reviewed in section 7.1.

7.2.1.1 Study type and design/patient enumeration

A list of the clinical studies to support safety is presented in the Table 27.

Table 27: Clinical Studies to Support Safety

Study Type	Study Number	Dose of Medication	Study Design	# Subjects
Phase I PK	S2300320	Mini lozenge 4 mg	Single dose 2 way crossover	29
Phase I PK	S2300339	Mini lozenge 1.5 mg	Multiple dose 2 way crossover	38
Phase I PK	S2300319	Mini lozenge 2 mg, 4 mg	Single dose 3 way crossover	35
Phase II PK	S3010567	Mini lozenge 2 mg, 4 mg	Single dose 4 way crossover	32
Phase II PK	S3010445	Mini lozenge 2 mg	Single dose 2 way crossover	28
Phase II PK	S3010466	Mini lozenge 4 mg	Single dose 2 way crossover	24

The studies are described in more detail in sections 4.1 and 4.2.

7.2.1.2 Demographics

Table 28 summarizes the demographic characteristics of subjects in the Phase I studies. Table 29 presents the demographic characteristics of the Phase II study subjects.

Table 28: Demographic Characteristics: Phase I Studies

	S2300319		S2300339	S2300320
	2 mg	4 mg	1.5 mg	4 mg
	(n= 20) n (%)	(n=15) n (%)	(n=44) n (%)	(n=30) n (%)
SEX				
Male	15 (75%)	9 (60%)	30 (68.2%)	21 (70%)
Female	5 (25%)	6 (40%)	14 (31.8%)	9 (30%)
RACE				
Asian	0 (0%)	0 (0%)	1 (2.3%)	0 (0%)
Black	0 (0%)	1 (6.7%)	7 (15.9%)	1 (3.3%)
Caucasian	19 (95%)	14 (93.3%)	34 (77.3%)	26 (86.7%)
Hispanic	0 (0%)	0 (0%)	0 (0%)	2 (6.7%)
Other	1 (5%)	0 (0%)	2 (4.5%)	1 (3.3%)
AGE (years)				
Mean (SD)	30 (11)	32 (9)	33 (11)	31 (11)
Min, Max	19,49	22,45	18,53	18,54

Table 29: Demographic Characteristics: Phase II Studies

	S3010445 (n=28) n (%)	S3010466 (n=28) n (%)	S3010567 (n=40) n (%)	Pooled (n=96) n (%)
SEX				
Male	24 (85.7%)	19 (67.9%)	27 (67.5%)	70 (72.9%)
Female	4 (14.3%)	9 (32.1%)	13 (32.5%)	26 (27.1%)
RACE				
Asian	28 (100%)*	0 (0%)	1 (2.5%)	29 (30.2%)
Black	0 (0%)	2 (7.1%)	3 (7.5%)	5 (5.2%)
Caucasian	0 (0%)	26 (92.9%)	34 (85.0%)	60 (62.5%)
Hispanic	0 (0%)	0 (0%)	1 (2.5%)	1 (1.0%)
Other	0 (0%)	0 (0%)	1 (2.5%)	1 (1.0%)
AGE (years)				
Mean (SD)	26.5 (6.2)	33.0 (10.0)	32.7 (9.8)	31.0 (9.4)
Min, Max	21.0, 43.0	20.0, 51.0	19.6, 55.9	19.6, 55.9
BMI (kg/m^2)				
Mean (SD)	22.0 (2.5)	23.9 (1.8)	23.5 (2.2)	23.2 (2.3)
Min, Max	19.0, 26.8	19.9, 26.7	19.1, 27.0	19.0, 27.0

*** All Subjects were Indian**

7.2.1.3 Extent of exposure (dose/duration)

The pharmacokinetic studies were single dose studies (with one exception). Table 30 summarizes the number of patients exposed in the Phase I and Phase II studies to the nicotine polacrilex mini lozenge. Study S2300339 did have a multi-dose component. This phase I study administered 13 doses of the 1.5 mg mini lozenge to a total of 42 patients.

Table 30: Single Dose Exposure to Nicorette Lozenge in Phase I and Phase II Studies

Dose	Study Number	# of Patients Exposed
2 mg Nicorette Lozenge	S3010567	38
	S2300319	19
	S3010445	28
Total		**85**
4 mg Nicorette Lozenge	S3010567	32
	S2300319	14
	S2300320	29
	S3010466	26
Total		**101**

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

This does not apply.

7.2.3 Adequacy of Overall Clinical Experience

Commit lozenge and other forms of nicotine replacement therapy have been marketed world-wide for many years. The overall clinical experience is extensive and the drugs are safe for over-the-counter use.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

This does not apply.

7.2.5 Adequacy of Routine Clinical Testing

This does not apply.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

This does not apply.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The principal areas for concern with the nicotine replacement products are the use in pregnant and nursing women and the use in adolescents under age 18. The use of nicotine in any form (including nicotine replacement products) is currently not recommended for pregnant or nursing women. Any change to this recommendation would require further studies and appropriate safety data.

Reviewer Comments: The use of NRT in pregnant and nursing women and in adolescents from ages 12 to 17 has not been adequately studied. An efficacy study in adolescents should be considered. It is unlikely (in this reviewer's opinion) that a definitive study in pregnant or nursing women could be completed.

7.2.8 Assessment of Quality and Completeness of Data

From a clinical safety perspective, the submission is complete.

7.2.9 Additional Submissions, Including Safety Update

There was no additional information provided.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

This does not apply.

7.4.2 Explorations for Predictive Factors

This does not apply.

7.4.3 Causality Determination

This does not apply.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

There will be no change in the dosing regimen or administration of Nicorette lozenge as compared to Commit lozenge. The patients are to select the dose based on the amount of time until they smoke the first cigarette of the day. Once the dose is established, patients are instructed to gradually use fewer lozenges according to the schedule in Table 31. Patients are advised not to smoke while using the lozenges and the goal for therapy is complete smoking cessation.

Table 31: Dosing Regimen for Nicorette lozenge

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

8.2 Drug-Drug Interactions

There were no additional data submitted in regards to drug-drug interactions. It is known that nicotine can interfere with the absorption of several medications via interaction with the CYP450 system and stopping smoking may consequently make some medications more (or less) effective and a dose adjustment may be required. The serum nicotine levels after smoking are generally

higher than after using NRT so these medications may blunt the effect of smoking cessation to some degree.

Medications that may have an increased serum level after smoking cessation include: Aminophylline, Beta-blockers, Prazosin, Propoxyphene, and Insulin. Medications that may have lower serum levels after smoking cessation include isoproterenol and phenylephrine. Package labeling for Nicorette directs consumers to discuss use of the product with their physician or pharmacist if they are taking medication for depression or asthma.

8.3 Special Populations

There are no additional studies on special populations included with this submission. The latest information regarding safety in pregnant or nursing patients is addressed in section 7.1.14. Use of nicotine replacement products is not recommended in pregnant or nursing women. There has been no evidence of a need for dose adjustment in those over age 60 though the studies in this population are limited. The NRT products are not recommended for those under age 18.

8.4 Pediatrics

Commit lozenges were initially approved before the Pediatric Research Equity Act (PREA) was mandated. The label states that patients under 18 should consult a physician prior to using the medication. The sale of Commit lozenges is restricted to consumers over age and there have not been adequate efficacy studies for use of Commit lozenges in patients under age18.

This submission only deals with a change the size of the lozenge. The active ingredient, indication, dosage form, and route of administration are unchanged. There were no clinical studies submitted and none requested. We agree that this submission does not trigger PREA.

Reviewer Comments: Misuse or abuse by those under 18 does not seem to be frequently reported. See sections 7.1.13 and 7.1.16 for additional information. Tobacco abuse in adolescents is a concern and the use of these products needs further study, particularly with regards to efficacy.

8.5 Advisory Committee Meeting

This does not apply.

8.6 Literature Review

GSK performed a literature search of four medical databases (Embase, Medline, Biosis, and Derwent Drug File) to find literature discussing the adverse affects, safety, and toxicity of nicotine gum or nicotine lozenges. Relevant articles published since 1993 were included. The search also focused on misuse and abuse of the NRT products by all users and also by pregnant and nursing women and by adolescents age 12 to 17. Articles related to other forms of NRT

(patches, inhalers) as well as general review articles on NRT, cigarettes, or tobacco dependence were not included.

A search focusing on new information regarding the abuse potential of the gum or lozenge found the following studies:

- The subjective effects of nicotine lozenge, including abuse liability and effects on craving were examined in 12 adults and 12 young adults (aged 18 to 21 years) in a randomized, double-blind, double-dummy, placebo-controlled, crossover study. Abuse liability of the lozenge was low in adults and young adults. Taste of the lozenge was rated lower than placebo and similar to the gum. The lozenge dose-dependently reduced cravings in adults but not younger adults. Results suggested that the lozenge has low abuse potential.[11]
- The rate of abstinence depending on length of therapy was studied in patients that wanted to quit. A total of 33 patients received Nicorette gum ad lib for 1 month and 28 for 3 months. There were minimal withdrawal symptoms when the gum was discontinued and no difference between the two groups. After 1 year, continuous abstinence was 42% in the 3 month group compared to 21% in the 1 month group.[12]
- Nicotine or placebo gum was assigned randomly to 315 patients who wished to quit smoking. In the nicotine group, 46% of the abstainers used gum beyond the recommended four months. In the placebo group, 17% used gum beyond the recommended four months. By 10 months, 17% of quitters in the nicotine group and 6% in the placebo group were still using gum daily. Gradual reduction of nicotine gum did not result in withdrawal and cessation of the gum did not increase probability of relapse.[13]
- In the Lung Health Study, heavy smokers with early Chronic Obstructive Pulmonary Disease who successfully used nicotine gum to quit smoking, 26% used the gum > 6 months. The authors concluded that nicotine gum contributed to success in smoking cessation but some smokers may need additional intervention.[14]
- One review focused on the relationship of nicotine dependence and nicotine tolerance. The authors conclude that chronic tolerance to nicotine is not closely associated with nicotine dependence; non-dependent and dependent smokers are equally tolerant. Tolerance declines very little even years after quitting and tolerance before quitting may have no relationship to clinical outcome of a cessation attempt. These results question the relevance of nicotine tolerance to dependence and suggest that research into mechanisms of tolerance, while important for understanding biological adaptation, may not elucidate factors responsible for nicotine dependence.[15]

Reviewer Comments: Use of the gum or lozenge for prolonged periods continues to be an issue. The safety of this is unknown.

A literature review was done by GSK focusing on new information on adverse effects, safety, toxicity, misuse, and abuse of the nicotine gum or lozenge by pregnant or nursing women. One review article[16] of the existing data was submitted by the sponsor. No new data were found in the article.

A literature search was done by GSK and two articles regarding general safety of NRT and four articles that focused on safety of NRT in patients with cardiac disease were reviewed. These are all summarized below.

- Although NRT is an aid for smoking cessation, many smokers alternate NRT with cigarettes. This study evaluated the cardiovascular effects of smoking and using nicotine gum. Concomitant gum plus smoking did not increase the incidence of arrhythmia and there were no signs of myocardial ischemia.[17]
- Long-term use of nicotine gum caused hyperinsulinemia and insulin resistance in a group of 20 otherwise healthy men.[18] The implications of these findings are not clear.
- In a double-blind crossover trial, nicotine gum caused increased heart rate in non-smokers compared to placebo but no significant increase in BP, skin temperature, or calf blood flow.[19]
- The effect of nicotine gum on hemodynamics and myocardial contractility was evaluated in 38 long-term smokers (15 with coronary artery disease, 2 with dilated cardiomyopathy, 21 controls). An insignificant increase in heart rate, cardiac output, and cardiac index was seen in the controls. Coronary patients showed a slight (insignificant) decrease in regional contractility in ischemic myocardial regions.[20]
- Patients with withdrawal symptoms may use simultaneously many sources of nicotine including transdermal patch, gum, and cigarettes and there was no effect on BP and a minimal increase in heart rate.[21]
- The effects of nicotine gum were examined on coronary artery dimensions in 17 heavy smokers with coronary artery disease. Nicotine gum did not decrease the cross-sectional area of coronary stenosis.[22]

The literature review submitted also included a review of two studies performed by GSK. These studies focused on the safety of the nicotine polacrilex lozenge and gum and are summarized below.

- Nicotine polacrilex lozenges deliver 25-27% more nicotine compared with nicotine polacrilex gum. This has raised questions regarding relative safety. This study compared the safety profile of the 4mg lozenge and the 4mg gum in smokers with selected label-restricted diseases. Patients were evaluated at baseline, 2, 4, 6, and 12 weeks after starting the product (447 received the lozenge and 454 received the gum). The incidence of adverse events between the two populations was similar through the entire study with no clinically significant differences. The most common adverse events were nausea, hiccups, and headache. GSK concluded that the 4 mg lozenge and 4 mg gum had comparable safety profiles in these patients.[23]
- To evaluate the pharmacokinetic characteristics of the 2 mg and 4 mg lozenges, four separate studies were done in healthy adult smokers: (a) A single-dose, four-way crossover study to compare the 4 mg lozenge and the 4 mg gum, (b) a single-dose, two-way crossover study to compare the 2 mg lozenge and the 2 mg gum, (c) a multiple-dose, four-way crossover study to compare the lozenges administered every 90 minutes and the gum administered every 60 minutes at the 2 mg and 4 mg dose levels, and (d) a singe-dose three-way crossover study to compare the pharmacokinetic profiles of the 4 mg lozenge when administered in three different ways: (i) used as directed, (ii) chewed and immediately swallowed, and (iii) chewed, retained in the mouth for 5 minutes, and then swallowed. The single-dose studies consistently showed 8-10% higher maximal plasma concentrations and 25-27% higher AUC

values for the lozenges as compared to the same dose of the gum. Despite this difference, the safety profile of the two formulations was similar. GSK also concluded that administration of the lozenge contrary to the label-specific directions for use did not lead to a faster or higher absorption of nicotine.[24]

The literature search also included several published individual published case reports. None of these reports included any significant or unexpected new adverse events.

Reviewer Comments: There were no studies or reports that had any unexpected adverse events or safety findings. The study by GSK showing a similar safety profile for the Commit lozenge even when not used according to the label directions (such as when chewed) is helpful when considering the faster dissolution time for the Nicorette lozenge and the concerns about absorption.

8.7 Postmarketing Risk Management Plan

No postmarketing plan was submitted.

8.8 Other Relevant Materials

There are no other relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

The Nicorette lozenge is bioequivalent to the currently marketed Commit lozenge. It has the same active ingredient and the same safety profile. The smaller size and faster dissolution time do not affect the action or safety of the medication.

9.2 Recommendation on Regulatory Action

Approval

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No special risk management activities are recommended.

9.3.2 Required Phase 4 Commitments

None

9.3.3 Other Phase 4 Requests

None

9.4 Labeling Review

The proposed labeling for the Nicorette lozenge is presented below. The labeling review is being done by the interdisciplinary scientist in the Division of Nonprescription Regulation Development. All of the appropriate warnings for nicotine replacement products were included.

9.4.1 Labeling of Nicorette lozenge 2 mg

The label is the same for the 2 mg and 4 mg doses except for the amount of nicotine polacrilex in each lozenge and the specific dosing instructions regarding dose size.

b(4)

1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

b(4)

9.5 Comments to Applicant

There are no additional comments.

10 APPENDICES

10.1 Review of Individual Study Reports

10.2 Line-by-Line Labeling Review

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