Adverse Events Leading to Discontinuation

Reviewer's Table 18

	Number (%) of Subjects			
	2mg Nicotine Lozenge n=459	**2mg Placebo Lozenge n=458**	**4mg Nicotine Lozenge n=450**	**4mg Placebo Lozenge n=451**
AEs leading to Discontinuation	31 (7%)	16 (4%)	33 (7%)	48 (11%)

[Based on sponsor's Table 6.2.1.1, p.89.]

A total of 7 % (128/1818) discontinued from Study S1410043 due to treatment emergent AEs. The most common causes for discontinuation were nausea, mouth soreness, diarrhea/flatulence, and heartburn. There were 13 subjects who discontinued due to nausea in the 2mg nicotine group and 8 subjects who discontinued due to nausea in the 4mg nicotine group. Nausea was generally considered to be treatment related. One subject discontinued due to flatulence in the 2mg group and 2 subjects discontinued from the 4mg group for the same reason. Over 90% of the flatulence cases were considered treatment related. Two subjects in both the 2mg and 4mg nicotine groups reported heartburn at the time of discontinuation. Among all cases of heartburn, it was considered treatment related between 80% and 97% of the time. Diarrhea was considered treatment related in 96% of the cases reported. One subject in the 2mg nicotine group discontinued due to sore throat.

[Item 6.2.2.2, pp. 92-95.]

Five subjects discontinued due to AEs in the 6 pharmacology studies. Two subjects in the 4mg nicotine group discontinued in Study N96016. One subject had an infected tooth and the other mild tachycardia. These AEs were not considered drug related. In Study S1410092 a subject in the 3mg nicotine lozenge group discontinued due to gingival bleeding, gingivitis, and stomatitis. In Study S1410091 in the 4mg nicotine gum group developed a rash and discontinued. In Study S1410089 one subject in the d-amphetamine group was discontinued after developing tachycardia, lightheadedness, and elevated blood pressure. All these were considered drug related. [Item 8.H.8.1, p. 347.]

Overall Evaluation of Adverse Events

Nausea, heartburn, headache, hiccups, and coughing were significantly greater among nicotine lozenge users compared to placebo. Other frequently occurring AEs in the nicotine group included flatulence and diarrhea. [Item 6.6, p.92-95, 121.]

Appropriateness of Adverse Event Categorization and Preferred Terms

This reviewer examined the raw data listings and compared them to the terms used in the Sponsor's table 6.3.1.2.1. A sampling of comparisons of AEs and preferred terms found the terms to be appropriate.

Laboratory Findings

There were no clinically significant changes to laboratory measurements in the pharmacology studies and there were no clinical parameters in Study S1410043.

Vital Signs

Vital signs were generally within normal ranges in the pharmacology studies with 2 exceptions. One subject in Study S1410089 has elevated blood pressure during amphetamine dosing and one subject in Study S1410090 has pulse rate $\geq$ 100 at several time points. No vital signs were collected in Study S1410043.

9 USE IN SPECIAL POPULATIONS

Adequacy of By-Gender Investigation and Analyses

In Study S1410043, there were 788 men and 1030 women. Women reported higher rates of AEs than men in all treatment groups did. The greatest difference between men and women was noted in the two nicotine groups.

Reviewer's Table 19

	PERCENT OF SUBJECTS			
	2mg		4mg	
	Nicotine Lozenge	**Placebo**	**Nicotine Lozenge**	**Placebo**
All (n=1818)	68%	56%	71%	52%
Men (n=788)	61%	54%	68%	52%
Women (n=1030)	73%	57%	74%	53%

[Based on Sponsor's Tables 6.2.4.2.1, p. 112-114.]

Women most commonly reported headache, diarrhea, flatulence, heartburn, hiccup, nausea, coughing and URTI. The proportions were similar to the ITT population but more women reported nausea, and depression than the general population. Women had a report rate of at least 5% for the following AEs: mouth irritation, viral infection, mouth ulceration, and depression in at least one treatment group.

Men most commonly reported headache, flatulence, hiccup, nausea, and URTI. The proportions were generally similar to the ITT but men reported a higher incidence of dry mouth and a lower incidence of nausea, depression and viral infection.

Men and women also generally reported similar AEs. However, men had a higher incidence of dry mouth and women had a higher incidence of depression, nausea, viral infection ,and coughing as compared to men.

His reviewer examined the data in Table 6,2,4,2,1 and did a representative comparison to data in Table 9.19.1.1 and found no discrepancies.

Elderly Population

Of the ITT population in Study S1410043, 302 (16.6%) were over 55. The incidence of AEs was slightly higher in the over 55 group (excerpt in the 4mg placebo group) than in those under 55.

Reviewer's Table 20

AGE	PERCENT OF SUBJECTS			
	2mg		4mg	
	Nicotine Lozenge	**Placebo**	**Nicotine Lozenge**	**Placebo**
All Subjects	68%	56%	71%	52%
<55 years	67%	55%	70%	54%
≥55 years	73%	61%	75%	47%

[Based on Sponsor's Tables 6.2.4.1.1, p. 109-111]

In subjects over 55 there was a generally higher proportion of reports of headache, nausea, flatulence, heartburn and URTI than in those under 55 or in the overall ITT population. In addition to these most common AEs, the over 55 group had a report rate of over 5% across all treatment groups for diarrhea, coughing, sore throat, depression, disturbed sleep, viral infection, sinusitis, and hiccup.

Ethnic Population

The Caucasian population of Study S1410043 was 94%. The sponsor notes that because the differences in sample size were so great, conclusions between ethnic groups should be made with caution. [Item 1.15, pp. 290-291.]

Reviewer's Table 21

RACE	PERCENT OF SUBJECTS	
	2mg	4mg

	Nicotine Lozenge	Placebo	Nicotine Lozenge	Placebo
All Subjects (n=1818)	68%	56%	71%	52%
Caucasian (n=1707)	69%	57%	72%	53%
Black (n=60)	48%	31%	47%	38%
Asian (n=14)	60%	33%	100%	100%
Other (n=37)	86%	63%	58%	40%

[Based on Sponsor's Tables 6.2.4.3.1, 15.4.1, pp. 115-116.]

Only one Black subject reported nausea and that was in the 4mg nicotine group. The most common AEs reported by Black subjects in the 2mg nicotine group were URTI and surgical intervention and in the 4mg nicotine group they were headache and URTI.

Three Asian subjects reported chest pain, flatulence, nausea, disturbed sleep, endometriosis, and pleurisy in the 2mg nicotine group. In the 4mg nicotine group 2 subjects reported headache, eructation, nausea, and vomiting.

Six subjects of other races in the 2mg nicotine group reported aggravated hypertension, dizziness, bloating, borborygmus (rumbling noise made by gas through the intestines), hiccup, mouth ulceration, nausea (2), disturbed sleep, coughing (2), headache, toothache, and URTI. In the 4 mg nicotine group 7 subjects reported headache, flatulence, dry mouth (3), mouth irritation (2), appetite increased, irritability, marked restlessness (2), pneumonia, respiratory disorder, atopic allergic rhinitis, sinusitis, and URTI. [Item 6.2.4.3, pp.114-116.]

10 Abuse Liability

The sponsor refers to earlier studies on nicotine gum by Henningfield, 1985 and Nemeth and Coslett, 1987 in which ratings for drug liking and MBG score showed no significant difference from placebo and indicated minimal or no abuse liability for the gum.

The sponsor then refers to Study S1410089 that was a single-dose, double-blind, placebo-controlled randomized crossover study in 24 subjects. In this study nicotine lozenges and 4mg Nicorette gum were compared to d-amphetamine using three standard abuse liability variables: Drug liking, positive effect, and the ARCI morphine benzedrine group (MBG or euphoria) sub-scale scores. All results for lozenges and gum were significantly less than d-amphetamine. Both the gum and the lozenge showed significantly less palatability than the confectionery lozenge. No difference in abuse liability was found between younger (mean age 20) and older (mean age 40) adults. The study concluded that had an abuse liability similar to the gum. The sponsor also refers to studies from the literature and recording of various indicators such as media tracking, the Safe and Drug Free Schools Coordinators Survey, and youth interviews that have had few reports of misuse or abuse by youth, non-smokers, or smokers. The sponsor also states their intent to implement a post-marketing surveillance program to continue to

collect data on misuse, abuse and dependence potential. This reviewer feels that the implementation of the post-marketing surveillance program should be an essential element in the approval process for this drug.
[Item 3.I.1, p. 473, Item 8.I, pp. 367-368.]

11 120-Day Safety Update

It should be noted that during the last 6 months of the study subjects were no longer using the lozenge. Nausea remained the most frequently occurring AE ranging from 12%-15 % in both nicotine groups followed by flatulence, diarrhea, heartburn, and hiccup in less than 10% of both nicotine groups. Because reports were minimal at 12 months for respiratory AEs, median number of lozenges used, and number of cigarettes smoked/day before quitting, the sponsor did not repeat these analyses. There was a discontinuation rate of 7% due to AEs and only one SAE reported earlier as possibly related to treatment. That was a case of an acute allergic reaction and windpipe constriction in the 2mg nicotine group that was considered highly probably related. The intensity was recorded as moderate and the patient recovered after discontinuing the lozenge. No new deaths were reported in the last 6 months of the study. [Item 9, pp. 19-20, Vol. 2, 12 month addendum, p. 5]

The abstinence rate at 12 months was 18% for the 2mg nicotine group versus 10% for the 2mg placebo group and 15% for the 4mg nicotine group versus 6% for the 4mg placebo group. This smoking rate was defined in the Safety Update as CO verified continuous abstinence at 12 months post-quit. While this rate is lower than at the previous time points, this decrease is to be expected and does not mitigate, in the opinion of this reviewer, against approval. [Vol. 1.2, p.49, 50.]

12 REVIEW OF PACKAGE INSERT

There is a concern about the labeling regarding the maximum number of lozenges a patient should use. The maximum number of lozenges allowed in the study were 20/day but the label is only written to allow a maximum [redacted] and to discontinue use of the lozenge at 12 weeks. After several discussions with Dr. Celia Winchell, Addiction Drug products Team Leader, and Dr. Stella Grosser, Biostat Reviewer it was felt that we are unable to determine the number of lozenges patients would actually take if the maximum was written [redacted] If this number was considerably lower than the numbers reported in the trial, the efficacy of the product could be affected. While it is true that there was a higher incidence of treatment emergent AEs in the 4mg group in those who took more than 15 lozenges/day, this may be a result of these subjects being more highly addicted and not a function of the increased use of the lozenge. Since the lozenge program is to be used for a limited amount of time and is considerably safer than smoking a cigarette, this reviewer concurs with the opinion that the label should reflect the way the drug was actually used in the trial. That is a maximum of 20 lozenges/day and continuing a dose of 1-2 lozenges/day for up to 6 months if needed to stay smoke-free.

The label and User's Guide warn about symptoms such as mouth problems, irregular heartbeat or palpitations, nausea, vomiting, dizziness, diarrhea, weakness, and rapid heartbeat. While nausea and diarrhea are consistent with the safety database, other AEs that occurred frequently in the nicotine group such as headache, flatulence, heartburn, hiccup, coughing, and sore throat are not included in the proposed draft label. These additional symptoms should, in the opinion of this reviewer, also be included. Upper respiratory tract infection (URTI) was considered unrelated to study drug. [Item 6.2.1, p. 94.]

13 CONCLUSIONS

The label and User's Guide mention reduction in withdrawal symptoms including nicotine craving. These claims are consistent with the results obtained in the first two weeks post-quit where there was a statistically significant reduction in both craving and overall withdrawal symptoms.

The safety and efficacy of nicotine polacrilex lozenge, 2 and 4 mg, has been demonstrated in this clinical trial. The sponsor has also stated that they plan to do a post-marketing surveillance program consisting of, "media and consumer tracking, theft surveillance, AE and complaint monitoring and the Drug Free Schools Coordinators Survey." It is the opinion of this reviewer that this NDA 21-330 can be approved from a clinical perspective provided the marked-up proposed draft labeling is agreed to by the sponsor and instituted, and that the sponsor also institutes and maintains their proposed surveillance program.

Harold Blatt D.D.S.
Clinical Reviewer

cc: Division File
Original NDA 21-330
HFD-170: McCormick, Winchell, etc.

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

/s/

Celia Winchell
10/9/01 01:49:27 PM
MEDICAL OFFICER
Primary Review by Hal Blatt, DDS. Entered into DFS for Dr. Blatt by Celia Winchell.

CLINICAL REVIEW

NDA 21-330
Nicotine Polacrilex Lozenge 2 mg and 4 mg
Glaxo Smith Kline

Celia Winchell, M.D.
Medical Team Leader
Division of Anesthetic, Critical Care, and Addiction Drug Products

OTC Review

NDA #:	21-330
Drug name (Generic Name):	Nicotine Polacrilex Lozenges, 2 mg and 4 mg
Sponsor:	SmithKline Beecham Consumer Healthcare
Pharmacologic Category:	Nicotine replacement, smoking cessation aid
Proposed Indication:	Reduction of withdrawal symptoms, including nicotine craving, associated with quitting smoking
Submission Date:	December 15, 2000
Review Date:	July 17, 2001

The sponsor submitted this NDA for OTC marketing of Nicotine Polacrilex lozenges, 2mg and 4mg, as an aid to smoking cessation. Currently, smokers have five choices of medications proven effective for quitting smoking: nicotine gum, nicotine patch, nicotine nasal spray, nicotine inhaler, and bupropion (Fiore et al., 2000). The gum and patch are available for OTC use. According to a 1998 Gallup Poll of current and former smokers, only 20% of smokers reported ever trying the OTC patch, and 16% ever trying OTC gum. SmithKline Beecham Consumer Healthcare (SBCH) has developed a new oral dosage form (Nicotine Polacrilex Lozenge) of nicotine replacement therapy. The lozenge is intended to appeal to a group of smokers who are motivated to quit, but would prefer an oral dose form of smoking cessation aid that is not a gum. They may be unable to use the gum or reject it as an option due to taste or dislike of chewing, or medical reasons (TMJ, fillings, or bridgework). These barriers may prevent smokers who wish to quit and use pharmacotherapy from obtaining effective tobacco dependence treatments. In foreign markets, a lozenge dosage form of nicotine replacement therapy is distributed which contains nicotine in the form of nicotine bitartrate (Nicotinell 1 mg). This lozenge was approved in 10 European countries in October, 1999. In addition, a 0.35 mg lozenge is approved in the United Kingdom. To the best of SBCH's knowledge, no country has requested that nicotine lozenges be withdrawn from the marketplace for safety concerns.

This NDA contains seven clinical trials that are being reviewed by HFD-170 and HFD-870: three single dose PK trials comparing lozenge to gum (S1410092, N98001, and N96016); one multiple-dose PK and bioavailability trial comparing 2 and 4mg lozenges to 2 and 4 mg gum at steady state (S1410091); a single dose, PK misuse trial (S141090); one pivotal, placebo controlled trial for safety and efficacy (S140043) and one abuse liability study (S1410089). Another study examining reactions and impressions among teenagers to the lozenge is being reviewed by HFD-170.

In addition to the trials just mentioned, the sponsor has submitted

- study S1410065 which is a randomized, open-label, two-way crossover study of subject expectation and acceptance of the lozenge,
- two label comprehension studies (2117 and 2204), and a
- home-use study S1410154.

Reviews of these studies follow.

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ON ORIGINAL

Study S1410065

This was a randomized, open label, two-way crossover study to measure subject expectations and acceptance of nicotine lozenges compared to Nicorette® nicotine gum in heavy smokers. The study was performed by [redacted] between July 30, 1998 and September 18, 1998. The study enrolled 219 subjects and exposed them to one dose each of nicotine lozenge and gum. After screening, each subject participated in the study for approximately 4 hours on a single day.

Two nicotine dosage forms were used during the study:

- 4 mg Test Nicotine Lozenge [Code Number 0129-2, Control Number 98Z080]
- 4 mg variant of NICORETTE® nicotine Gum [Lot #ZC715A, Batch Number ZC638]

Objectives

The primary objective of this study was to measure subject expectations and acceptance of a test nicotine lozenge compared to original flavor NICORETTE® gum in heavy smokers. The secondary objective was to gather a qualitative indication of the expectations and acceptance of a test nicotine lozenge compared to NICORETTE® gum in heavy smokers represented in the following immigrant ethnic subgroups: Chinese, Russian, Polish, Indian and Latinas, as well as a subgroup of US-born subjects. Immigrant subjects were pre-screened to include subjects who emigrated from their country of origin at or over the age of ten (10) years old.

Study Design

The planned number of subjects was 216. Two hundred and nineteen (219) subjects were enrolled into the study. Criteria for inclusion and exclusion are listed below :

Inclusion criteria

- Healthy male and non-pregnant female volunteers aged 18+ years of age.
- Heavy (>24 cigarettes/day) smokers.
- Motivated to participate in a study to evaluate nicotine products.
- Understands the study and is willing to participate as evidenced by voluntary written informed consent. Able to read and understand the English language.
- Able to refrain from smoking for the duration of the study.

Exclusion criteria

- Positive urine pregnancy test (on the day of study).
- Clinically significant abnormal findings during the screening physical examination or medical history.

- History of any clinically significant disease, which in the opinion of the investigator would jeopardize the safety of the subject.
- Inability to abstain from smoking during the study medication treatment period.
- Inability to abstain from eating anything other than the study medications and drinking anything other than water during the study medication treatment period.
- Oral surgery or extraction within 6 weeks prior to study initiation.
- Dentures or any dental work that could affect the conduct of the study, including missing molars.
- Any oral pathology including lesions, sores or inflammation.
- History of allergic response to nicotine gum or nicotine transdermal patches or any nicotine products.
- Phenylketonurics.
- Hypersensitivity to nicotine or nicotine polacrilex or any of the following ingredients: Aspartame, calcium polycarbophil, flavors, glycerin, gum base, mannitol, magnesium stearate, sodium alginate, sodium carbonate, sorbitol, potassium bicarbonate, Xanthan gum, D&C yellow 10.
- Inability to comprehend the procedures to be used during the study as determined by the investigator on screening.
- Member or relative of the study site staff directly involved with the study, or employee of sponsor.
- Previous enrollment in this study.

Study Procedure

Prior to enrollment, each subject was screened, received a brief physical examination, gave a medical history and gave voluntary written informed consent. Female subjects of childbearing potential completed a urine pregnancy test. On the study day, the subject was given instructions on the correct procedure for ingestion of the test nicotine lozenge and for chewing NICORETTE® gum. The subject was randomized to receive either one lozenge or one piece of gum. The dose was dissolved (or chewed) for 20 minutes according to the instructions. The lozenge (or gum) was then collected and discarded, and a taste-rating questionnaire was administered to the subject. After a 1-hour washout period, the subject was given the other of the test drugs (the one not previously administered). After 20 minutes, the second test drug was again collected and discarded, and a taste-rating questionnaire was given. After a final assessment for adverse events, the subject was released from the site by the investigator. Prior to each dose, and after the last dose, the subject was given 2 non-salted crackers and 4 ounces of water to clear the palate of flavors.

Subjects were not allowed to take any medications during the study confinement period. Subjects were not allowed any food or water, other than what was provided by the study

staff during the study. Tobacco use was not allowed during the confinement period of the study.

Table A1 summarizes the study procedure.

Table A1. Flow Chart of Investigations [S1410065 Study Report, P 6]

Investigations	Pre-Screen	Pre-Dose	Dose 1	Wash-out**	Dose 2	Post Dose
Telephone Contact Questionnaire	X					
Subject Screening Questionnaire	X					
Demographics and Medical History	X					
Inclusion/Exclusion Criteria	X					
Physical Examination	X					
Pregnancy Test		X				
Review of chewing/ingestion procedure		X		X		
Crackers and Water Intake		X		X		X
Dosing*			X		X	
Taste Rating Questionnaire			X		X	
AE Assessment				X		X

* 1st dose will be either test nicotine lozenge or NICORETTE® gum depending upon randomisation schedule, 2nd dose will be the medication not used for 1st dose.
** Interval period of drug administration was 80 minutes.

Subject Disposition

Subjects were stratified into one of the six ethnic categories at the clinical study site according to information provided during the pre-screen telephone screening questionnaire: Russian, Polish, Indian, Chinese, Latina, or native US. Following stratification, the subject was randomized to both study products in terms of the dosage form sequence order.

Table A2: Subject Disposition [S1410065 Study Report, P 19]

Subjects enrolled	219
Completed study	213
Did not complete study	6
Protocol violations	3[a]
Adverse event	2[b]
Consent withdrawn	1[c]
Incorrect Stratification	3[d]

[a] Subject 115 was discontinued after receiving one piece of gum due to a protocol violation. (Not a heavy smoker). Subject 116 was discontinued after receiving one piece of gum due to a protocol violation. (Not a heavy smoker). Subject 210 was discontinued after receiving one piece of gum due to a protocol violation (Had extreme difficulty reading questionnaire)
[b] Subject 112 was discontinued due to an adverse event after receiving one piece of gum. Subject 507 was discontinued due to an adverse event after receiving one piece of gum.
[c] Subject 117 withdrew consent after receiving one piece of gum.
[d] Subject 512 was excluded from efficacy analysis due to incorrect stratification. Subject 513 was excluded from efficacy analysis due to incorrect stratification. Subject 527 was excluded from efficacy analysis due to incorrect stratification.

The subjects' disposition is summarized in Table A2 shown above. Of the 219 subjects enrolled into the study, 6 subjects were excluded from the intent-to-treat analysis. Subjects 112 and 507 were discontinued due to adverse events experienced after receiving one piece of gum. Subjects 115, 116 and 210 were discontinued due to a protocol violation that was discovered after receiving one piece of gum. Subjects 115 and 116 were discovered to be light smokers only and Subject 210 exhibited extreme difficulty in completing the questionnaire. Subject 117 withdrew consent after receiving one piece of gum. These subjects were not included in the intent-to treat analysis because of incomplete data.

All subjects excluded from the intent-to-treat analysis were also excluded from the efficacy-evaluable population. Three (3) additional subjects were excluded from the efficacy-evaluable population because of incorrect ethnic group stratification.

MO Comment: *Since there was only one study site, it is possible that the population studied in this trial is not representative of the OTC population who would use this product.*

Demographics

Of the 219 subjects enrolled into the study, there were 92 females (42%) and 127 (58%) males. The mean age at enrollment was 33.7 years. The gender ratios differed among subgroups, with Indian and Russian smokers mainly male, but US smokers predominantly female (see Table A3 below).

MO Comment: *Gender ratios were not representative of the OTC population.*

Table A3: Demographic Characteristics

Ethnic Classification	Chinese	Indian	Russian	Polish	Latina	U. S. Born
Participants Total = 210	39	38	34	37	24	38
Mean Age[1]	31.4	28.7	32.3	38.5	31.9	39.6
SD[2]	11.8	8.6	11.3	8.7	9.1	10.5
Male	19 (44.2%)	35 (89.7%)	30 (81.1%)	14 (58.3%)	23 (60.5%)	6 (15.8%)
Female	24 (55.8%)	4 (10.3%)	7 (18.9%)	10 (41.7%)	15 (39.5%)	32 (84.2%)

[1] Mean age calculated from the date of birth provided by the subject

[2] Standard Deviation

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Results

The primary analysis included 210 subjects. The primary study parameter was the subject's expectations and acceptance of the lozenge as compared those for the gum. The gum served as the control in this study to which all lozenge responses were compared on a statistical basis.

A questionnaire was administered after each dosage form was tasted. For each question, frequency distributions and medians for the test nicotine lozenge, NICORETTE® gum, and the scored difference (lozenge minus gum on an intra-subject basis) were calculated for each ethnic group separately, and for all subjects independent of ethnic classification. The Wilcoxon Signed Rank test was used to test the differences at the alpha=0.05 level, between the two products when the differences exceeded one or two response grades. If the differences were only a grade or two, a sign test was used, calculating binomial probabilities. A significance level of 5% was considered in evaluating the results of all statistical tests. Descriptive statistics were provided for the demographic characteristics, calculated for each ethnic group separately, and for all subjects independent of ethnic classification. Since the sample sizes of the subgroups were not large enough to indicate statistically significant differences, data trends were examined.

The primary study parameter was the subject's taste expectations and acceptance of the lozenge compared to the gum after tasting both dosage forms. Data from questions relating to overall expectation (Q1), flavor liking (Q2), flavor level intensity (Q3), comfort of dose mass (Q6), ease of instructions (Q8), voluntary compliance (Q10), overall experience (Q14) and perceived efficacy (Q16) were used for efficacy evaluation. Results generated from the analyses are summarized in Table A4.

Table A4. Expectation and Experience Ratings (S1410065)

	Lozenge N=214 Mean (± SD)	Gum N=217 Mean (± SD)	p-value Wilcoxon test (sign test)
Q1. expectations (range 1-3; 2= as expected)	2.08 (± 0.76)	2.08 (± 0.70)	0.92 (0.66)
Q2. flavor (range 1-9; 5=neutral, 6=slight dislike)	5.18 (± 2.04)	5.29 (± 2.05)	0.36 (0.44)
Q6. comfort (range 1-6; 2=moderate comfort)	2.16 (± 1.16)	2.37 (± 1.18)	0.04 (0.06)
Q7. How many minutes in mouth	14.32 (±10.3)	15.44 (±11.2)	0.27 (not given)
Q8.* Directions (range 1-7; 5=moderately easy, 6=very)	5.26 (± 1.38)	5.81 (± 1.16)	< 0.001 (< 0.001)
Q10.* Use per day (range 1-5; 3 = "4 to 6 times")	3.22 (± 1.17)	3.01 (± 1.18)	0.02 (0.04)
Q14. Overall (range 0-10; 10 ="extremely pleasant"	4.54 (± 2.63)	4.59 (± 2.47)	0.56 (0.83)

*significant difference between lozenge and gum

Question #1: Compared to what you might have expected from this type of product, how would you rate the experience?

1 = Better than expected
2 = About as expected
3 = Not as good as expected

There was no significant difference (see Table A4) between the post-usage expectation for either product, with both the lozenge and gum experience rated as "about as expected". Additionally, none of the sub-groups exhibited any differences between the post-usage expectation for either product, with both the lozenge and gum experience also rated as "about as expected".

Question #2: How much would you say you like the taste/flavor of this product?
1= Like it extremely 2= Like it very much
3= Like it moderately 4= Like it slightly
5= Neither like or dislike it 6= Dislike it slightly
7= Dislike it moderately 8= Dislike it very much
9= Dislike it extremely

There were no significant differences observed in the total sample population (see Table A4) or any sub-group for ratings of flavor liking between the lozenge and the gum. The mean scores for this question indicate that all participants either felt neutral (neither like nor dislike) or disliked the flavor/taste slightly. The flavor was rated better by participants of Chinese (4.73 lozenge, 4.52 gum) and Indian (4.84 lozenge, 4.79 gum) origin, than by participants in the Russian (5.57 lozenge, 5.97 gum), Polish (5.21 lozenge, 5.08 gum), Latina (5.38 lozenge, 5.29 gum) or US-born (5.42 lozenge, 6.08 gum) contingents.

MO Comment: *The slightly unpleasant taste of the lozenge, which was rated by study participants to be very similar in taste rating to that of the gum, is a favorable finding - a taste too unpleasant could discourage use, but a taste too appealing could possibly encourage abuse.*

Question #6: [Gum] How do you feel about the comfort of the "parked" piece of gum? Was it...? [Lozenge] How do you feel about the shape, was it...?

1= Very comfortable in your mouth
2= Moderately comfortable in your mouth
3= Only slightly comfortable in your mouth
4= Slightly uncomfortable in your mouth
5= Moderately comfortable in your mouth
6= Very uncomfortable in your mouth

Only the US-born Americans gave significantly different comfort ratings for the two products. The US-born group felt that the lozenge was significantly more comfortable than the gum (p=0.003), and the other subgroups exhibited the same trend, producing the combined group p = 0.04 by Wilcoxon test (0.06 by sign test).

Question #7: Approximately how many minutes do you think you would keep this lozenge/gum in your mouth if you were using it to control your craving to smoke?

There was no significant difference (see Table A4) between the reported time the lozenge and the gum would be voluntarily held in the mouth. Participants in the study indicated they would keep the lozenge in their mouths an average of 14.32 minutes, while the gum would be held for an average of 15.44 minutes.

Question #8: How did you feel about following the instructions for using this product?

1= Found following the instructions extremely difficult.
2= Found following the instructions very difficult.
3= Found following the instructions moderately difficult.
4= Didn't find the instructions either difficult or easy.
5= Found following the instructions moderately easy.
6= Found following the instructions very easy.
7= Found following the instructions extremely easy.

MO Comment: *The use directions for the lozenge were rated in Q8 as significantly easier ($p<0.001$) to follow than those for the gum, although both were rated as moderately to very easy.*

Question #10: Based on experience with this product, how many times do you think you would use it per day to help you curb your craving for a cigarette if you decided to stop smoking? If the label said you could use 1 (Gum: piece of gum, Lozenge: lozenge) every 1 to 2 hours, would you use it...?

1= 10-12 times 2= 7-9 times 3= 4-6 times 4= 1-3 times 5= 0 times

Subjects indicated that they would likely use the products *an average* of 4-6 times per day. Participants of Indian and Latina origin reported that they would use significantly more gum than lozenge (3.37 lozenge vs. 2.95 gum, p=0.04, Indian; and 3.51 lozenge vs. 2.97 gum, p = 0.03, Latina). In the other sub-groups, mean scores were not significantly different for lozenge and for gum.

MO Comment *The mean score for lozenge (3.22) was higher than that for gum (3.01), indicating that participants would use more gum than lozenges, rather than the reverse as stated in the study report. In addition, the p-values for the ethnic subgroups are not consistent with the combined group value for Q10 reported in Table A4 from the Sponsor's analyses. However, the differences amounted to only a fraction of a unit on a 5 point categorical scale, and are not clinically meaningful.*

In addition, subjects were asked which of the dose forms they preferred (Table A5, responses to question 13).

Table A5. Preferred Product (Q13): Number (%) of Subjects

Ethnic Classification	All subjects combined	Chinese	Russian	Polish	Latina	US-born
Preferred Gum	117 (54.9)	24 (61.5)	19 (51.4)	15 (62.5)	22 (59.5)	14 (36.8)
Preferred Lozenge	70 (32.9)	12 (30.8)	15 (40.5)	6 (25.0)	10 (27.0)	17 (44.7)
Other	26 (12.2)	3 (7.7)	5 (13.2)	3 (12.5)	5 (13.5)	7 (18.4)

MO Comments: *A preference for the gum was seen in all ethnic groups except for US-born, which was predominantly female. The gender difference may have confounded this result.**Question #14: Overall, how would you describe your experience with the product?***

0 to 10 scale with 0=Not at all pleasant and 10= Extremely pleasant

The lozenge mean rating was 4.54 and the gum mean rating was 4.59 for this question. No significant difference was noted in subgroup analyses of ratings of the pleasantness associated with using the lozenge or the gum (see Table A4). All sub-groups means indicated that subjects considered the experience with both products to be slightly unpleasant.

Safety Evaluation

The safety analysis evaluated the incidence of adverse events and discontinuations because of adverse events, and included all 219 subjects who received both forms of study medication.

Adverse events

Of the 219 enrolled subjects who received study drugs, 135 subjects (61.6%) experienced a total of 256 adverse events. Of the 256 adverse events, 241 (94.1%) were considered mild or moderate in intensity, and 253 (98.8%) were considered probably or definitely related to the study drug.

The most commonly reported adverse event was tingling, numbing, burning, or an uncomfortable feeling in mouth, throat or esophagus (48.0%). These adverse events are known to be related to nicotine dosage forms and not unexpected. Dizziness, headache, nausea, vomiting were also reported. Most of these events were characterized as mild or moderate in intensity and probably or definitely related to study medication. All resolved without sequelae. There were no significant differences between the frequency and intensity of the reports between the treatment groups.

Two subjects (0.91%) withdrew from the study because of an adverse event: one participant, Subject 112, experienced dizziness, thirst and vomiting following use of the first dose (NICORETTE® gum). The dizziness was thought by the investigator to be probably related to the study medication, while the thirst and vomiting were thought as definitely related to the study medication. Subject 507, experienced generalized itching, nausea, scant vomiting, tightness in neck and jaw and pain in chest radiating to shoulder following use of the first dose (NICORETTE® gum), which the investigator thought was possibly related to the study medication, with the exception of nausea and scant vomiting which was thought to be definitely related to the study medication.

There were no deaths or serious adverse events during the study. Unexpected adverse events or unexpected adverse event frequencies were not observed during the study.

Discussion and Overall Conclusions

There were no perceived differences between the test nicotine lozenge and the NICORETTE® gum in terms of acceptance, and no shifts in the expectations post-usage for either product as evidenced by the data collected for the questions relating to expectations, flavor liking, and overall experience. The participants indicated that based on their experience with both dosage forms, they would use significantly more gum per day than lozenges. The overall study population also rated the gum as having a stronger flavor level, but there was no significant difference in overall pleasantness between the two dosage forms. In addition, the participants found the instructions for use of the gum to be significantly easier to follow than the instructions for the test nicotine lozenge ($p< 0.001$).

The overall adverse event rate was consistent with those found in previous nicotine trials.

The lozenge met the overall study population's expectations and was as equally accepted when compared to the gum. The product usage experience was rated the same (slightly unpleasant) for both dosage forms.

No differences were noted on analysis of subgroups for rating of flavor liking between lozenge and gum. The mean scores for this question indicated that all participants either felt neutral or disliked the flavor/taste slightly. However, ratings for Chinese and Indian participants were slightly more positive than for Russian, Polish, Latina or US-born participants.

MO Comments *This was primarily a marketing study. The safety experience was favorable in that there were no significant differences between the frequency and intensity of the reports between gum and lozenge; however, the exposure to the drug was limited to single doses of 4 mg lozenge and 4 mg gum in 219 subjects. The time without cigarettes was too short for nicotine withdrawal symptoms to peak (typically after several days), so perceived efficacy and user satisfaction may be less in actual use. There were no notable differences in acceptance between gum and lozenge.*

Subjects stated that they would use the gum more frequently than the lozenge, but the difference was only 0.2 on a categorical scale of 1 to 5, with the means for both gum and

lozenge in the "4 to 6 per day" category. This data is of limited relevance to the present NDA, because the subjects were not screened as to intention to stop smoking and were also not exposed to complete label directions.

The equivalence in taste ratings between gum and lozenge is favorable because it gives no reason to expect that the lozenge will exceed the gum in abuse potential on the basis of flavor preference.

APPEARS THIS WAY
ON ORIGINAL

Nicotine Lozenge Label Comprehension Study Protocol No. 2117

This was a label comprehension study performed by [redacted] The primary objectives of this study were:

- to evaluate how well the average smoker understands the conditions (i.e. uses and directions) in which he/she can use the lozenge,

- to ensure consumers can self-select the appropriate dose based on when they smoke their first cigarette of the day.

Differences in comprehension were evaluated between the representative population of smokers and the low-literacy population of smokers. Adults with a low literacy level were included to determine whether the label is clear to those who read at a maximum 7^{th} or 8^{th} grade level. Interviews were conducted in nine geographically dispersed markets. A total of 272 interviews were conducted. Interviewing for this study began on September 1 and ended on September 7, 2000.

Study Design

Interviews were conducted at ten sites in nine geographically dispersed locations. Respondents were intercepted on shopping center malls and screened for qualifications. Some respondents were intercepted at convenience stores, neighborhood grocery stores, and apartment complexes to recruit low-literacy adults.

Those qualified and willing to participate were escorted to a separate area to be interviewed. The respondents were shown the front package panel for both dosage levels of the product and then asked which dosage they should personally use. The back label of the dosage level the respondent chose was then shown to the respondent, and he/she was asked to read it. Questions were then asked about the label to determine respondents' understanding of how to use the product in a safe and effective manner. Respondents were encouraged to refer back to the label at any time.

There were two cohorts in this study:

- Representative smokers
- Low literacy smokers

Low-literacy respondents found in the representative population were included in the low-literacy cohort. In order to be classified as low literacy, a respondent must read at a maximum 7^{th} - 8^{th} grade level as determined by the Rapid Estimate of Adult Literacy in Medicine (REALM) literacy screening instrument. The REALM test is administered to the respondent in a non-threatening manner.

Respondents were given a color copy of the product package label. The copies of the labels were the actual size of the package label.

Inclusion and exclusion criteria

Inclusion criteria for the representative cohort were:

- age at least 18 years.
- smoke cigarettes on a regular basis.

To be enrolled as a low-literacy smoker, subjects had to meet all of the requirements for the representative portion of this study listed above, **and**

- Read at a maximum 7th-8th grade equivalency level as determined by the Rapid Estimate of Adult Literacy in Medicine (REALM) literacy screening instrument.

Subjects were excluded from the study if:

- they or anyone in their household worked in the marketing research field, in an ad agency/public relations firm, a pharmaceutical company, as a healthcare professional, or as part of a health care practice.
- participated in a marketing research study regarding healthcare products in the past 3 months.
- normally used corrective lenses, contacts or glasses to read and didn't have them with them.

Table B1. Study Population Enrolled [Study Report 2117, P 10]

Representative Population	Low Literacy Population	Total Interviews
200	115	272

A total of 272 interviews were conducted, divided between cohorts as shown in Table B1. The number of interviews shown for each cohort does not add up to the total number of interviews conducted due to the low-literacy respondents in the representative population also counting toward the low-literacy population.

Understanding of Product Uses

Table B2 shows clear understanding that the product is for smoking cessation. Numbers in the tables are percentages of the cohort in each column. The correct subnet is the percent of initially correct answers. The acceptable subnet is the additional percentage of answers that were not on the label but were still acceptable.

Table B2: "Based on the Label, What is this Product Used For? Or in Other Words, Why Would Someone Use this Product?" (Q.3) [Study Report 2117, P 12]

	Representative Population, N = 200 Column a (%)	Low Literacy Population, N = 115 Column b (%)
Correct (Subnet)	**99**	**97**
To quit /stop smoking	83b[1]	69
To reduce withdrawal symptoms to quit/stop smoking	15	26a
To reduce withdrawal symptoms – To quit/stop smoking	1	2
To reduce withdrawal symptoms	-	1
Acceptable (Subnet)	**1**	**2**
Nicotine withdrawal	1	-
Get rid of habit	1	1
Make you not want to smoke	-	1
Correct / Acceptable (Net)	**100**	**99**
Incorrect (Net)	**1**	**1**
Help cut down smoking	1	1

[1]Note: If a letter appears next to a number (i.e, 83b), then the letter means that number is significantly greater than the number in the **same row** in the column represented by the letter. All tables have been tested at the 95% confidence level using t-stat testing.

Appropriate Self-selection

During the screening process, consumers were asked how soon after waking they typically smoke their first cigarette. This question was asked among other questions relating to smoking as well as among other non-smoking related questions. The non-smoking related questions were asked only to "mask" the importance of the "when smoke first cigarette" question.

In the label interview, respondents were told to assume that they *do* want to use this product and that they are in the store getting ready to buy the product. Respondents were shown the front label of both the 2 mg and 4 mg package and then asked which dosage level they should personally use. Their answers were compared with their classification to determine the percentage of respondents who correctly or incorrectly understood the label direction regarding dosage selection.

All respondents were asked their reasons for their dosage selection, and the reasons from those who were initially incorrect were reviewed. Most of these answers were still incorrect. However, some of these respondents gave a correct answer to their dosage selection. For example, in screening if a respondent said he/she smoked within 30 minutes of waking, he/she was classified as "4 mg". Then, when asked what dosage level he/she should personally use, he/she was marked as "incorrect" if he/she responded with "2 mg". However, if his/her reason for choosing the 2 mg dosage was "because I don't smoke within 30 minutes of getting up" or "I don't smoke until after lunch", this person

was assessed as having a correct understanding of the label and his/her status was changed from being "incorrect" to "acceptable".

Table B3 shows that consumers in both populations had a fair understanding (overall correct or acceptable 81%) of which dosage level they should personally use.

Table B3: "Based Only on What These Labels Tell You, Which Dosage Level Should You, Yourself, Use? In Other Words, Which One of These Packages Should You, Yourself, Use?" (Q.1) [Study Report 2117, Taken from Table 2 P 14]

	Representative Population			Low Literacy Population		
	Total	Smoke >30 minutes after waking (2 mg)	Smoke within 30 minutes of waking (4 mg)	Total	Smoke > 30 minutes after waking (2 mg)	Smoke within 30 minutes of waking (4 mg)
	a	b	c	d	e	f
Base: Total in each group	200	93	107	115	54	61
Correct (Subnet) %	80	76	83	84	83	84
2 mg	36	76c	-	39	83f	-
4 mg	45	-	83b	44	-	84e
Acceptable after Probe (Subnet) %	1	1	1	4	4	3
Smoke first cigarette more than 30 minutes after waking	1	-	1	2	-	3
Smoke first cigarette within 30 minutes of waking	1	1	-	3	4	-
Correct/Acceptable (Net) %	**81**	**77**	**84**	**87**	**87**	**87**
Incorrect after Probe (Net) %	19	23	16	13	13	13
Smoke first cigarette more than 30 minutes after waking	5	9c	1	3	6	-
Smoke first cigarette within 30 minutes of waking	4	1	7	3	-	5
Stronger dose more effective/more medicine works faster	2	4c	-	2	4	-
Do not want to take too much medicine/don't know how it will effect me	2	-	3	1	-	2
Don't smoke immediately after waking/can wait awhile	1	2	-	1	-	2

Note: If a letter appears next to a number, then the letter means that number is significantly greater than the number in the **same row** in the column represented by the letter.

In addition to the initial self-selection question where respondents were asked which dosage they should personally take, two scenarios were tested that described someone who should select a 2 mg dose and someone who should select a 4 mg dose.

Card C says: You are over 18 years old and you want to quit smoking. You typically don't smoke your first cigarette until after you've been awake for two hours. You definitely want to use the product to help you quit smoking.

The responses to this scenario are shown in Table B4; overall correct or acceptable responses 82%.

Table B4: "Based on the Label You Just Read, if You Were This Person, Which Milligram Dosage of This Product Should You Use?" (Card C, Q.7) [Study Report 2117, P 15]

	Representative Population	Low Literacy Population
	a	b
Base: Total in each group	200	115
2 mg (Correct %)	**82**	**82**
4 mg (Incorrect %)	18	15
Don't know (Incorrect %)	1	4a

The second scenario (Card D) outlined below led to a similar result, with correct or acceptable responses at 86% as shown in Table B5.

Card D says: You are over 18 years old and you want to quit smoking. You typically smoke your first cigarette 5 minutes after waking up. You definitely want to use this product to help you quit smoking.

Table B5: "Based on the label you just read, if you were this person, which milligram dosage of this product should you use?" (Q.8) [Study Report 2117, P 15]

	Representative Population	Low Literacy Population
	a	b
Base: Total in each group	200	115
4 mg (Correct %)	**86**	**81**
2 mg (Incorrect %)	15	17
Don't know (Incorrect %)	-	3a

For the remainder of the interview, respondents were given a booklet of cards describing people in different situations. They were told to pretend that they were the person described on each card. They were also told to assume that the people described in the cards did not have any of the conditions listed on the label that would prevent them from using this product. The respondents were encouraged to refer to the label at any time during the interview.

MO Comment: *The rates of appropriate self-selection of the dosage level were in the range of 77% - 87% which would be acceptable if no significant safety concerns were revealed in a well conducted "all-comers" actual use trial.*

Use Directions

While only a moderate number of respondents (72%) in the representative population seemed to understand that a User's Guide was enclosed in the box, the level of understanding of this fact among the Low Literate population was better (82%). Consumers did understand that this product should be used for 12 weeks (correct

respondents, 98% of representative group vs 94% of low literacy group). Nine out of ten consumers from both cohorts understood that on the first day of the program, one lozenge should be used every 1-2 hours.

In the representative cohort, 83% understood that after using the drug for 4 weeks, one lozenge should be used every 1-2 hours. However, understanding this concept among Low Literate adults was significantly lower at 70%. Most of those who answered this incorrectly responded with "every 2 to 4 hours" (see Table B6 below).

Table B6. Frequency of use, end of first 4 weeks. (Card F) [Study Report 2117, P 20]

	Representative Population	Low Literacy Population
	a	b
Base: Total in each group	200	115
Correct (Net %)	**83b**	**70**
Incorrect (Net %)	18	30a
One every 2–4 hours	14	19
One every 4–8 hours	2	2
No more than 9 per day	1	-
Use the same as before	-	2
Don't know	2	7a

Note: If a letter appears next to a number, then the letter means that number is significantly greater than the number in the same row in the column represented by the letter.

MO Comment: *Consumers in the low literacy group had difficulty understanding the frequency of dosing after 4 weeks of use and most often chose the same rate for weeks 7-9.*

However, both populations had a good understanding (88% correct) that during weeks 7 to 9 of the program, one lozenge should be used every 2-4 hours. Likewise, both populations had a good understanding that during weeks 10 to 12 of the program, one lozenge should be used every 2-4 hours (representative population 92% correct vs low literacy population 90% correct).

Nearly all respondents understood that the lozenge should be placed between the cheek and gum, or on one side of the mouth (representative population 96% correct vs low literacy population 92% correct). There was adequate understanding that after about one minute, the lozenge should be moved to the other side of the mouth (representative population 92% correct vs low literacy population 84% correct).

A high level of understanding that the lozenge cannot be swallowed was demonstrated, especially among the representative population cohort (95% correct). The level of understanding of this concept among Low Literate adults was significantly less (85% correct). However, most of those Low Literate adults who were not correct said they did not know. Similarly, for the scenario in Card L, 94% of the representative group knew that a lozenge which has been in the mouth for about 5 minutes and which has not completely dissolved should not be chewed. However, a significantly smaller fraction (79%) of low literacy adults understood this, and 14% did not know the answer.

MO Comment: *Since the AUCs and C_{max} are lower when the product is swallowed or chewed, these alternate methods of ingestion would not result in a safety issue although efficacy could be affected. (See HFD-870 Division of Biopharmaceutics review, 7/26/01)*

The scenario in Card M referred to someone wanting to use a lozenge ***after*** drinking coffee. Respondents did not understand that a lozenge could be used *after* drinking coffee as demonstrated by less than half of the Representative Population and only one-quarter of the Low Literate respondents answering this question correctly (see Table B7 below).

Table B7:"According to the Label, If You Were This Person, is it Okay or not Okay to Use a Lozenge After Finishing a Cup of Coffee?"(Q.19, Card M) [Study Report 2117, P 24]

	Representative Population	Low Literacy Population
	A	b
Base: Total in each group	200	115
OK (Correct %)	**43b**	**24**
Not OK (Incorrect %)	48	63a
Don't know (Incorrect %)	10	13

Note: If a letter appears next to a number, then the letter means that number is significantly greater than the number in the same row in the column represented by the letter.

MO Comment: *There was much confusion about use of the drug after drinking coffee, which is a situation in which consumers commonly feel an urge to smoke. Again, this confusion may compromise efficacy since consumers could resume smoking rather than use a lozenge.*

Respondents' understanding was 86% to 89% regarding the need to use at least 9 lozenges per day for the first 6 weeks to increase one's chances of quitting as shown in Table B8.

Card N says: You have been using this product for 4 weeks.

Table B8: "According to the Label, To Improve Your Chances of Quitting, You Should Use *At Least* How Many Lozenges Per Day?"(Q.20, Card N) [Study Report 2117, P 25]

	Representative Population	Low Literacy Population
	A	b
Base: Total in each group	200	115
Nine: Correct (Subnet %)	**79**	**77**
Acceptable (Subnet %)	**10**	**10**
No more than 20 per day	4	4
Twelve	3	4
Twenty	2	1
No more than 20 per day-	1	-
One every 1-2 hours	1	1
Correct/Acceptable (Net %)	89	86
Incorrect (Net %)	12	14
Three	2	2
Two	2	3
Six	2	-
Don't know	4	7

Respondents had a strong understanding that only one lozenge can be used at a time (representative population 91% correct vs low literacy population 86% correct with 5% of the low literacy population who did not know). Nearly all respondents understood that lozenges can not be continuously used right after another (representative population 98% correct vs low literacy population 95% correct). Consumers had a reasonable understanding (representative population 88% correct vs low literacy population 80% correct) that a maximum of twenty lozenges can be used in one day. In addition, one percent of those who answered this incorrectly stated a number greater than twenty (the highest answer was 45, from a member of the representative population). Most incorrect answers were too low a number.

Understanding was demonstrated to be strong among consumers that after 12 weeks one should see a doctor if he/she still feels the need to use the lozenges (representative population 93% correct vs low literacy population 90% correct).

MO Comment: *This study was adequately designed and implemented. It demonstrated that a significant fraction of both the general population and low literacy consumers (up to 23%) chose the incorrect dose form. However, this would not be a concern if no safety issues are revealed in a well-conducted all-comers actual use trial.*

It would have been helpful to include scenarios testing whether consumers understood that people with cardiovascular conditions should consult a physician prior to using the product.

The Sponsor's use of time to smoking the first cigarette after waking as the criterion to determine the choice of dose form appears to be satisfactory. Table B9, shows that the numbers of cigarettes smoked per day is strongly but not perfectly correlated to the time to smoking the first cigarette after waking. The percent of smokers who used 1-5 cigarettes per day was found to be significantly greater in those who first smoke > 30 minutes after waking in both study cohorts. The percent of smokers who used 26-50 cigarettes per day was also found to be significantly greater in those who first smoke <30 minutes after waking in both study cohorts.

Table B9: "About How Many Cigarettes Do You Smoke Per Day?"(S.12)

[Study Report 2117, Taken from Table 22 P 29]

	Representative Population			Low Literacy Population		
	Total	Smoke >30 minutes after waking (2 mg)	Smoke within 30 minutes of waking (4 mg)	Total	Smoke > 30 minutes after waking (2 mg)	Smoke within 30 minutes of waking (4 mg)
	a	B	C	d	e	f
Base: Total in each group	200	93	107	115	54	61
1-5 cigarettes (%)	16	29c	5	13	26f	2
6-10 cigarettes (%)	24d	25	22	14	15	13
11-25 cigarettes (%)	49	42	55	64a	57b	69c
26-50 cigarettes (%)	11	3	17b	9	2	15e
51or more cigarettes (%)	1	1	1	1	-	2

Note: If a letter appears next to a number, then the letter means that number is significantly greater than the number in the same row in the column represented by the letter.

The study revealed two areas in which comprehension needs to be improved. The first is the rate at which the dose per day should be tapered over time that was shown to be a problem in the low literacy group (Refer to Table B6). Evidently this concept was too complicated and confusing to this group. The second area of low comprehension was the use of the lozenge after drinking (see table B8). Use in association with meals was not tested. The concept that the lozenges should not be chewed or swallowed was both unfamiliar and confusing to a significantly larger fraction of low literacy consumers (15% to 20%) than general population consumers (5-6%).

Most errors in comprehension could lead to underuse (not using the drug at optimal frequencies or times) and/or potential loss of efficacy (from chewing and/or swallowing), rather than overdose.

Nicotine Lozenge Label II Comprehension Study 2204

This second label comprehension study was completed by [redacted] to verify understanding of a modified label that reduced maximum lozenge per day usage from 20 to 15. The second label comprehension study also corrected the wording of a question concerning use of the product while eating or drinking. The objectives, design, and eligibility/ineligibility criteria were the same as in the other label study (protocol 2117).

Interviews were conducted in nine geographically dispersed markets. A total of 272 interviews were conducted. Interviewing for this study began on October 24, 2000 and ended on November 1, 2000.

A total of 272 interviews were conducted, divided between cohorts as shown in Table C1. The number of interviews shown for each cohort does not add up to the total number of interviews conducted due to the fact that the low-literacy respondents in the representative population were also counted as part of the low-literacy population.

Table C1. Study Population [Study Report 2204, P 10]

Representative Population	Low Literacy Population	Total Interviews
200	125	272

Understanding of Product Uses

Consumers clearly understood that the lozenge is used to help one quit or stop smoking as shown in Table C2.

Table C2: "Based on the Label, What is this Product Used For? Or in Other Words, Why Would Someone Use this Product?" (Q.3) [Study Report 2204, P12]

	Low Literacy Population, N = 125 Column b (%)	Representative Population, N = 200 Column a (%)
Correct (Subnet)	**99**	**100**
To quit /stop smoking	78	81
To reduce withdrawal symptoms to quit/stop smoking	21	18
To reduce withdrawal symptoms – To quit/stop smoking	-	1
To reduce withdrawal symptoms	-	1
To quit/stop smoking	1	-
Correct / Acceptable (Net)	**99**	**100**
Incorrect (Net)	**1**	-
Help cut down smoking	1	-

Appropriate Self-selection

Consumers had a fair understanding of when one should take the 2 mg versus when one should take the 4 mg dosage as listed in Table C3, with 82% correct/acceptable for the representative group, and a significantly higher rate, 91% correct/acceptable, in the low literacy group.

Table C3: "Based Only on What These Labels Tell You, Which Dosage Level Should You, Yourself, Use? In Other Words, Which One of These Packages Should You, Yourself, Use?" (Q.1) [Study Report 2204, P14]

	Representative Population			Low Literacy Population		
	Total	Smoke >30 minutes after waking (2 mg)	Smoke <30 minutes of waking (4 mg)	Total	Smoke >30 minutes of waking (2 mg)	Smoke <30 minutes of waking (4 mg)
	a	b	c	d	e	f
Base: Total in each group	200	78	120	125	47	78
Correct (Subnet) %	**81**	**80**	**83**	**89a**	**89**	**89**
2 mg	31	80c	-	34	89f	-
4 mg	50	-	83b	55	-	89e
Acceptable (Subnet) %	2	3	1	2	6f	-
Smoke first cigarette more than 30 minutes after waking	1	-	1	-	-	-
Smoke first cigarette within 30 minutes of waking	1	3c	-	2	6f	-
Correct/Acceptable (Net) %	**82**	**82**	**83**	**91a**	**96b**	**89**
Incorrect after Probe (Net) %	**18d**	**18e**	**17**	**9**	**4**	**12**
Smoke first cigarette within 30 minutes of waking	6d	-	8bf	1	-	1
Stronger dose is more effective/Has more medicine	4	9c-	-	1	2	-
Not as strong/Lower dosage/Safer	2	-	3	3	-	5
That's what label/guide says	2	1	2	-	-	-
Smoke first cigarette more than 30 minutes after waking	2	4c	-	-	-	-
Start with low dose then go to higher	1	-	2	2	-	3

Note: If a letter appears next to a number, then the letter means that number is significantly greater than the number in the same row in the column represented by the letter.

Two scenarios were tested that described someone who should select a 2 mg dose and someone who should select a 4 mg dose. For the first scenario (same as Card C of Study 2117), correct or acceptable responses totaled 87% for the representative cohort and 90% for the low literacy cohort. For the second scenario (Card D, Study 2117), correct or acceptable responses totaled 91% for the representative cohort and 90% for the low literacy cohort.

Use Directions

The study results demonstrated that there was weak understanding that a User's Guide is enclosed in the box (representative population 69% correct vs low literacy population 78% correct, which was found to be significantly different). However both cohorts understood that a consumer cannot smoke at all after starting the program (representative cohort 93% correct vs low literacy cohort 95% correct), and that this product should be used for 12 weeks (representative cohort 98% correct vs low literacy cohort 90% correct).

Nearly nine out of ten consumers understood that on the first day of the program, one lozenge should be used every 1½ to 2 hours (representative cohort 89% correct vs low literacy cohort 87% correct). The most common incorrect answers were "don't know" (representative cohort 3% vs low literacy cohort 7%) or a frequency that was too low (5% of representative cohort).

Two questions tested how often to use the product. The first question (Card F) described a scenario of someone in the fourth week of using the product, and asked respondents to state how often one should use a product at this point. The second question (Card M) described a scenario of someone in their fifth week of using the product, who had not taken a lozenge for 2 hours. This scenario asked whether the person could use another lozenge at this time.

When asked how often the product should be used after the 4th week, the representative cohort had a fair understanding (85% correct, Table C4) that one lozenge should be used every 1 ½ -2 hours . However, understanding among Low Literate adults was significantly lower at 72%. Most of the incorrect answers were "every 2 to 4 hours".

Table C4: "According to the Label, How Often Should You Use This Product Now?" (Q.12, Card F) [Study Report 2204, P20]

	Representative Population	Low Literacy Population
	A	b
Base: Total in each group	200	115
Correct (Net %)	**85b**	**72**
Acceptable (Subnet %)	**1**	**1**
Eight times a day	1	1
Eight more weeks	1	-
Incorrect (Net %)	**15**	**27a**
One every 2–4 hours	8	11
One every 4–8 hours	3	2
Don't know	1	12a

Note: If a letter appears next to a number, then the letter means that number is significantly greater than the number in the same row in the column represented by the letter.

However, when respondents were asked to state whether someone during week 5 of use could take another lozenge after two hours (Card M), both populations understood the program that it would be okay to use another lozenge at this time (representative cohort 88% correct vs low literacy cohort 91% correct).

Both populations had a fair to good understanding that during weeks 7 to 9 of the program, one lozenge should be used every 2-4 hours (representative cohort 89% correct vs low literacy cohort 83% correct). Incorrect answers tended in the direction of underdosing more than overdosing; 7% of the low literacy cohort answered "don't know".

Both populations understood that during weeks 10 to 12 of the program, one lozenge should be used every 4-8 hours (representative cohort 94% correct vs low literacy cohort 86% correct) although the understanding of this concept was significantly better in the representative group. The same was true for the question asking where in the mouth the lozenge should be placed (representative cohort 93% correct; low literacy cohort 86% correct), and for the question asking what to do with the lozenge after one minute (move to other side: representative cohort 95% correct vs low literacy cohort 88% correct).

There was strong understanding that the lozenge cannot be swallowed in the representative cohort (93%) but was found to be significantly less in the low literacy cohort (78%). A similar level of understanding was found in the scenario of Card L (whether to chew an incompletely dissolved lozenge after 5 minutes): representative cohort 91% correct vs low literacy cohort 80% correct. However, respondents in both cohorts understood that one cannot use a lozenge *while* drinking (representative cohort 93% correct vs low literacy cohort 94% correct).

On the question (Card O) regarding the need to use at least 8 lozenges per day for the first 6 weeks, Table C5 shows that understanding was fair in the representative cohort (86% correct/acceptable) but significantly lower in the low literacy cohort (72%).

Card O says: You have been using this product for 4 weeks.

Table C5: "According to the Label, To Improve Your Chances of Quitting, You Should Use *At Least* How Many Lozenges Per Day?"(Q.23, Card O) [Study Report 2204, P28]

	Representative Population	Low Literacy Population
	A	b
Base: Total in each group	200	125
Eight: Correct (Subnet %)	**75b**	**64**
Acceptable (Subnet %)	**11**	**8**
Fifteen	4	2
Twelve	3	2
Ten	2	1
No more than 15 per day	2	2
Nine	1	-
Twelve to fifteen	1	1
Fourteen	1	-
Correct/Acceptable (Net %)	**86b**	**72**
Incorrect (Net %)	**14**	**28a**
Six	3	2
One	2	2
Two	2	2
Four	1	2
Don't know	4	16a

*Note: If a letter appears next to a number, then the letter means that number is significantly greater than the number in the same row in the column represented by the letter.

In the representative cohort, respondents had a strong understanding (95% correct) that only one lozenge can be used at a time, but understanding was significantly less in the low literacy cohort (81%). Nearly all respondents understood that lozenges cannot be continuously used right after another (representative cohort 99% correct; low literacy 98% correct).

In the representative cohort, 88% understood that a maximum of fifteen lozenges can be used in one day. A significantly lower fraction (74%) of the low literacy cohort answered correctly. However, among those consumers answering incorrectly, no one stated a number greater than fifteen.

Understanding was strong in both cohorts (representative population 92% correct vs low literacy population 90% correct) that after 12 weeks one should see a doctor if he/she still feels the need to use the lozenges.

Table C6 shows the distribution of the number of cigarettes smoked per day versus the time to smoking the first cigarette after waking, in both cohorts. The results are similar to those in Table B9.

Table C6: "About How Many Cigarettes Do You Smoke Per Day?"(S.12)

[Study Report 2204, Taken from Table 23 P33]

	Representative Population			Low Literacy Population		
	Total	Smoke >30 minutes after waking (2 mg)	Smoke within 30 minutes of waking (4 mg)	Total	Smoke > 30 minutes of waking (2 mg)	Smoke <30 minutes of waking (4 mg)
	a	b	c	d	e	f
Base: Total in each group	200	78	120	125	47	78
1-5 cigarettes (%)	9d	21ce	1	3	9f	-
6-10 cigarettes (%)	28d	47ce	15	16	28f	9
11-25 cigarettes (%)	43	30	51b	65a	64b	65c
26-50 cigarettes (%)	20	1	32bf	13	-	21e
51or more cigarettes (%)	1	-	1	1	-	1
No answer	1	1	1	2	-	4

Note: If a letter appears next to a number, then the letter means that number is significantly greater than the number in the same row in the column represented by the letter.

MO Comment: *These two label studies are nearly identical in their design and results. The following changes were made in the label directions tested in the latter study: the minimum and maximum numbers of cigarettes per day* [redacted] *respectively. The areas of weak comprehension were also similar for both studies. A problematic scenario in Study 2117 (see Table B7) was replaced by a different question with a much higher rate of correct responses. This improvement was not attributable to any improvement in the label. In the study report the Sponsor implied that the question in the first study was poorly worded.*

APPEARS THIS WAY
ON ORIGINAL

Study 1410154

This was an open-label, uncontrolled, multi-center, home-use study to evaluate subject acceptance of nicotine lozenges, performed by [redacted] Subjects were recruited by mall intercept and self-selected to use either the 2 mg or 4 mg nicotine lozenge. Subjects used the product at home for two weeks and then participated in a follow-up telephone interview. Subjects were instructed to record product usage, adverse events, and concomitant medications in a diary. After the two-week use period, the subjects were required to return the diary, unused product, and product packaging.

A total of 408 subjects enrolled in the study and 212 completed it. There were 234 subjects who used the product and were analyzed for safety. The demographics, product usage, concomitant medications, and adverse events reported were summarized and tabulated. No statistical testing was performed on the safety data.

The following formulations were tested in this 2 week home-use study:

Nicotine lozenges, 2 mg, oral, OE22S

Nicotine lozenges, 4 mg, oral, OE42S

Active ingredient: nicotine polacrilex.

Inactive ingredients: mannitol, sodium alginate, calcium polycarbophil, sodium carbonate [redacted], xanthan gum, potassium bicarbonate, [redacted], aspartame

Study Design

Objective

The objectives were to assess safety in a home use setting, to evaluate perceived consumer satisfaction as well as to forecast the market volume potential of nicotine lozenges.

Procedure

Subjects were recruited at 54 sites located in shopping malls in 41 cities. Shoppers were intercepted by mall agency staff and asked a few marketing-based screening questions. If answers to the screening questions met study criteria, prospective subjects were shown a concept board and interviewed by agency staff. Those who were smokers and were willing to take the product and use it according to the labeling instructions were given the opportunity to participate in the clinical portion of the study. The study procedure is shown in Table D1.

These prospective subjects were screened through a telephone interview by a study nurse and a physician for inclusion/exclusion criteria as well as medical and medication history. Once informed consent was obtained, the signature page of the informed consent form was faxed to the study nurse at the [redacted] before product was dispensed to the subject. A birth control agreement was obtained from female participants of childbearing potential.

Subjects were asked to self-select the dose (2 or 4 mg) based on the information provided in the concept board. Subjects were provided a carton of selected product (108 count) and were

instructed to use the test product according to the package instructions. They were also instructed to record product usage, concomitant medications, and adverse events on a diary provided.

After the estimated 2-week use period, subjects received telephone contacts from a [redacted] interviewer. [redacted] was the market research company that handled the mall intercepts and telephone interviews for this study. Subjects were instructed to return the diary, unused product, and product packaging at the end of the use period. There was one physician designated as the principal investigator for the study and a number of local physicians located in the vicinity of each site to see subjects if necessary.

Table D1. Study Procedures [S1410154 Study Report, P 14]

Event (Responsibility)	Day 1 (Start)	Day 14* (Study Completion)
Shopping Mall Intercept (Agency)	X	
Concept Interview (Agency)	X	
Qualification Interview ([redacted] Nurse) Medical History Medication History Inclusion/Exclusion Criteria Demographics	X	
Informed Consent Signed (Agency [redacted] Nurse)	X	
Birth Control Agreement Signed (Agency/[redacted] Nurse)	X	
Test Product Dispensed [redacted] Nurse / Principal Investigator, Subinvestigator / Agency)	X	
Test Product Used as Needed (Subject)	X [redacted]	X
Diary Dispensed (Agency [redacted] Nurse)	X	X
Diary Completed (Subject)	X [redacted]	X
"Call-back" Interviews [redacted]	X [redacted]	X
Unused Product, Product Packaging Material and Diary Returned to [redacted] (Subject)		X[2]
Product Usage Evaluation, Concomitant Medication Review, Adverse Event Evaluation and Product Accountability Performed [redacted]		X[2]

[1]Subjects were called after the two week usage period.
[2]To be performed after use, at the end of Week 2, or later.
*Estimated to be a 2-week home use period.

[S1410154 p6]

Inclusion Criteria

To be considered eligible for enrollment into the home use, clinical portion of the study, subjects must meet the following inclusion criteria:

1. respond to the Concept Interview with one of the following answers: definitely would buy the product; probably would buy the product; might or might not buy the product;

2. be a smoker who is willing to take the product home and use it according to the labeling instructions;

3. be considered by the shopping mall research agency (Agency) interviewer, the — — — nurse, and either the Principal Investigator or a Sub-investigator to be motivated to participate in and complete the study as instructed;

4. understand and sign an informed consent form;

5. be in good health as assessed by a medical history conducted by a —— nurse and the Principal Investigator or Sub-investigator (a physician);

6. be male, or a non-pregnant, non-breast feeding female, of any race, and at least 18 years of age. Females of child-bearing potential must have been established on an acceptable method of contraception (including hormonal birth control, IUD, double barrier methods, or vasectomized partner) and signed a birth control agreement indicating they had been on an acceptable method of birth control for the last two months and which method they have been using. Females who are not of child-bearing potential must be either surgically sterile or 2 years or more post menopausal;

7. be willing and able to use the test product and complete the diary as instructed, participate in the follow-up telephone interview, and return the unused product, product packaging material and diary at the end of the study.

Exclusion Criteria

Subjects are excluded from the study if they:

1. are pregnant or breast feeding;

2. currently use forms of tobacco other than cigarettes such as pipes, cigars, snuff, or smokeless tobacco, or are planning to use these during the study;

3. have used any other smoking cessation treatment within 30 days of study entry;

4. have a known hypersensitivity to nicotine products;

5. have participated in any investigational drug study within the last 30 days;

6. have any other medical condition or situation, which constitutes a safety concern;

7. are not considered to be a good candidate to participate in and complete this study;

8. have a history of cardiovascular disease, ulcer disease, or diabetes;

9. have a genetic deficiency with an inability to metabolize aspartame or phenylalanine or has been diagnosed with phenylketonuria (PKU);

10. is a member of the same household as another clinical subject enrolled in this study, or is a relative of study site staff or a member of the study staff.

MO Comment: *Individuals at high risk (e.g., with cardiovascular disease, ulcers and diabetes) were excluded from this study. Nicotine by virtue of its ability to excite both the*

sympathetic and parasympathetic nervous systems at the same time, can cause vasoconstriction in various organs and limbs. Nicotine has sympathomimetic effects that can lead to increases in heart rate and blood pressure and cause coronary vasoconstriction. The increased incidence of duodenal ulcer among cigarette smokers may be due to inhibition of pancreatic bicarbonate secretion by nicotine or to accelerated emptying of gastric acid into the duodenum. Thus, individuals with peripheral vascular disease due to diabetes, cardiovascular disease or history of gastric ulcers may be at an increased risk for worsening of their underlying medical conditions by nicotine. Hence, these high risk individuals should not be excluded from an actual use trial if they choose to participate, since they may purchase these products and because they may benefit from smoking cessation.

In addition, exclusion criterion 7 is too vague and could potentially introduce selection bias into the study.

Each subject self-selected the study medication, 2 or 4 mg, based on the information made available to them via the concept board. The concept board had the following statement regarding dose: those smoking less than 24 cigarettes per day (cpd) should use the 2 mg lozenges and those smoking more than 24 cpd should use the 4 mg lozenges.

Use of any other smoking cessation treatment or investigational drug within 30 days prior to study entry was prohibited. Consent to continue the established, acceptable method of contraception was obtained from females of childbearing potential prior to study entry. Subjects were instructed to not smoke while using the nicotine lozenge.

MO Comment: *This study did not evaluate the product's label directions for use as proposed by the sponsor. In this study, the criterion for self-selection was based on the number of cigarettes smoked per day rather than the time to lighting up for the first cigarette of the day. In addition, the instruction not to smoke while using is potentially biasing, since the study was expected to determine whether subjects would follow the label direction not to smoke while using the drug without physician intervention. This study also did not report any use data (see below).*

The study supply of 108 lozenges was insufficient for 14 days' use according to either of the labels in the label comprehension studies: in Study 2117, the minimum and maximum numbers of lozenges per day were 9 and 20, respectively, while in Study 2204 these numbers were 8 and 15, respectively.

Disposition of Subjects

A total of 408 subjects were enrolled in the study, and 212 subjects (52%) completed the study as per protocol. A total of 234 subjects (57%) out of 408 enrolled subjects used the product, whereas 197 subjects (93%) out of 212 subjects who completed the study used the product. Disposition of the enrolled subjects is summarized in Table D2.

Table D2. Subject Disposition [S1410154, p24]

Subject enrolled	408
Product used	234
Completed study per protocol	212
Product used	197
Reasons for not completing the study	
Lost to follow up	117
Inappropriate enrollment	51
Adverse event	25
Non-compliance	3

MO Comment: *A large number of participants (28.7%) were lost to follow-up.*

Demographics

The mean age of enrolled subjects was 34 years of age (range 18-77) with a similar distribution between male and female (51%:49%). The majority (75%) of subjects were Caucasian. The demographics for all enrolled subjects and subjects who were evaluated for safety are summarized in Table D3.

Table D3. Demographics [S1410154, p25]

Variables	All Subjects Enrolled	Safety Subjects
No. of Subjects	408	234
Age	33.84 ± 12.78	34.19 ± 12.31
Gender	Male 51%, Female 49%	Male 44%, Female 56%
Race	Caucasian 75% African-American 12% Hispanic 5% Native American 4%	Caucasian 78% African-American 9% Hispanic 5% Native American 4%

Protocol Deviations

Fifty-one subjects did not complete the study per protocol since they were considered to be inappropriately enrolled. Three subjects were noncompliant with the protocol. Out of 408 subjects enrolled, 60 subjects did not use the product and 199 subjects did not return the lozenges. One subject, Subject 40-08001 reported that she did not use her birth control method while participating in the study, as she was not sexually active. Therefore, even though the subject technically did not follow the protocol requirement, this deviation did not lead to a safety concern.

MO Comment *The study report did not explain why 51 subjects were considered to be inappropriately enrolled. This is potentially a large enough number to affect the results. Another concern is the large fraction (199/408, 49%) of subjects who did not return the drug as directed since use of the drug could not be confirmed for these subjects. The study report did not include pill count data for those who did return unused study drug.*

Safety Evaluation

A total of 234 subjects used at least one dose of nicotine polacrilex lozenge. A summary of adverse events is provided in Table D4.

Table D4. Summary of Adverse Events [S1410154, p26]

No. of Subjects	234
No. of Events Reported	185
No. of Subjects Reporting Events	104 (44%)
Severity	Mild 93 (50%) Moderate 73 (39%) Severe 18 (10%) Unknown 1 (0.5%)
Relationship	Highly probable 61 (33%) Probable 46 (25%) Possible 45 (24%) Unlikely 21 (11)% Not related 12 (6%)

MO Comment: *Some of these subjects may have taken only one dose. No information was provided as to the number of doses taken or the days on which doses were taken. Likewise, the report did not investigate any possible relationship between the number or frequency of doses and the number and/or severity of AEs. There were 25/234 subjects who discontinued because of AEs (11%, a high proportion). Details on the patients who discontinued were not provided by the Sponsor in the study report.*

Adverse Events (AEs)

Out of 234 subjects who used the study drug, 104 subjects (44%) reported at least one adverse event for a total of 185 adverse events. Adverse events were listed as reasons for not completing the study in 25 of the 196 subjects who did not complete the study. Among the 185 adverse events reported, the body system most frequently affected was digestive system (27%), followed by nervous system (10%), respiratory system (10%), and body as a whole (8%). Among the individual adverse events listed, nausea (11%) was the most frequently reported adverse event, followed by stomatitis (9%), pharyngitis (6%), dyspepsia (6%), and dizziness (5%). The body system distribution of AEs is given in Table D5 found on the following page.

Most adverse events were either mild (50%) or moderate (39%) in severity. A total of 18 adverse events (10%) were severe in nature. The adverse events with severe rating were nausea (3), dyspepsia (3), increased cough (2), followed by headache, diarrhea, anorexia, mouth ulceration, stomatitis, abnormal dreams, anxiety, dizziness, laryngismus and taste perversion, all reported once each.

A total of 82% of adverse events reported were considered highly probably to possibly related to the use of study medication. Subjects managed all adverse events appropriately by discontinuing the use of medication or by self-treating with other therapy.

There were no deaths and no other serious or significant adverse events reported from the subjects who used the nicotine polacrilex lozenges in this study.

Table D5. Adverse Events by Body System

[taken from Tables 3 and 4 of S1410154 Study Report, P33-37]

Body System[a]	Total (185)	Severe (18)
Body as a Whole	**19 (8%)**	**1 (<1%)**
Abdominal pain	5 (2%)	0 (0%)
Asthenia	1 (<1%)	0 (0%)
Headache	9 (4%)	1 (<1%)
Infection	1 (<1%)	0 (0%)
Malaise	2 (1%)	0 (0%)
Pain	3 (1%)	0 (0%)
Cardiovascular System	**1 (<1%)**	**0 (0%)**
Tachycardia	1 (<1%)	0 (0%)
Digestive System	**64 (27%)**	**9 (4%)**
Anorexia	1 (<1%)	1 (<1%)
Diarrhea	3 (1%)	1 (<1%)
Dry mouth	6 (3%)	0 (0%)
Dyspepsia	13 (6%)	3 (1%)
Eructation	1 (<1%)	0 (0%)
Flatulence	1 (<1%)	0 (0%)
Gingivitis	2 (1%)	0 (0%)
Mouth ulceration	1 (<1%)	1 (<1%)
Nausea	25 (11%)	3 (1%)
Stomatitis	20 (9%)	1 (<1%)
Thirst	2 (1%)	0 (0%)
Tongue disorder	4 (2%)	0 (0%)
Tongue edema	1 (<1%)	0 (0%)
Ulcerative stomatitis	3 (1%)	0 (0%)
Vomiting	1 (<1%)	0 (0%)
Nervous System	**23 (10%)**	**3 (1%)**
Abnormal dreams	1 (<1%)	1 (<1%)
Anxiety	6 (3%)	1 (<1%)
Dizziness	11 (5%)	1 (<1%)
Facial paralysis	1 (<1%)	0 (0%)
Insomnia	2 (1%)	0 (0%)
Nervousness	8 (3%)	0 (0%)
Paresthesia	1 (<1%)	0 (0%)
Thinking abnormal	1 (<1%)	0 (0%)
Respiratory System	**24 (10%)**	**3 (1%)**
Cough increased	5 (2%)	2 (1%)
Hiccup	6 (3%)	0 (0%)
Laryngismus	1 (<1%)	1 (<1%)
Pharyngitis	13 (6%)	0 (0%)
Skin	**5 (2%)**	**0 (0%)**
Acne	1 (<1%)	0 (0%)
Application site reaction	2 (1%)	0 (0%)
Dry skin	1 (<1%)	0 (0%)
Pruritus	1 (<1%)	0 (0%)
Vesiculobullous rash	1 (<1%)	0 (0%)
Special Senses	**4 (2%)**	**1 (<1%)**
Taste perversion	4 (2%)	1 (<1%)

a Counts reflect numbers of subjects reporting one or more adverse events that map to the COSTART body system. At each level of summarization (body system or event) subjects are only counted once.

MO Comment: *There were no serious adverse events reported in this "home use" study, the majority of those reported were mild to moderate in severity. The profile of reported adverse events was consistent with those of other oral nicotine replacement products. However, high risk patients (i.e., participants with cardiovascular or ulcer disease, diabetes, or those with any other medical condition or situation which constituted a safety concern) were excluded from study entry. Additionally, the study was only 2 weeks long in duration and the Sponsor is proposing that this product be labeled for 12-weeks of continuous use.*

This study did not provide information on self-selection, compliance with label directions (the lack of pill counts at the end of the study of returned unused study medication), or use of the product in the OTC environment based on the Sponsor's proposed label (time to first cigarette versus the number of cigarettes smoked per day). Absence of this information severely limits the usefulness of this data. The study's criteria for dose selection was based on the number of cigarettes smoked per day rather than on the level of nicotine addiction as per the Sponsor's proposed labeling instructions. Thus, it is not possible to conclude from this study that consumers will self-select this product appropriately and use it safely and effectively.

Discussion and Overall Conclusions

In support of the safety portion of this application, the Sponsor submitted the results from seven clinical studies, a teen research study examining reactions to the lozenge, two label comprehension studies, one single-dose crossover marketing study, and a home use study. This OTC review concentrated on the results generated from the label comprehension, marketing and home use studies. (Refer to the HFD-170 and HFD-870 reviews for addition safety information regarding this NDA application.)

Although the marketing study revealed that consumers who participated in this trial did not favor the nicotine lozenge over the gum, the amount of safety information generated by this study was limited by the fact that only a single-dose was administered to healthy individuals. Despite this, the findings from the study were reassuring since the potential for product abuse was apparently not increased by the flavor of the lozenge. User satisfaction with the nicotine lozenge may in fact be less than what the results showed since the time without cigarettes was too short for nicotine withdrawal symptoms to become obvious in the study participants.

The results from the Sponsor's labeling comprehension studies raise concerns related to the ability of low literacy consumers to use the proposed tapering schedule appropriately. The risk for not using the product appropriately could result in diminished efficacy and lead to prolonged or chronic usage of the product (i.e., greater than the proposed 12 weeks). The label studies also did not test consumers' understanding of the need to consult a physician prior to using the product if they had heart disease. Further, the design of the home use study did not assess consumers' ability to appropriately self-select the correct dosage of medication. Without this important information, this reviewer is unable to determine if consumers can self-select this product appropriately and subsequently use it safely and effectively if it becomes available OTC.

NDA 21-330
Nicotine Polacrilex Lozenge
GlaxoSmithKline

120 day safety update addressed in page 35 of Medical Officer review.

Judit Milstein
8-31-01

APPEARS THIS WAY
ON ORIGINAL