CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-330

MEDICAL REVIEW(S)

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Clinical Review for NDA 21-330

Executive Summary

Nicotine polacrilex lozenge (2 mg and 4 mg) is a buccally delivered nicotine replacement product intended for use as an aid to smoking cessation. The clinical development program consisted of pharmacokinetic characterization of the product, comparison to the approved nicotine polacrilex gum (Nicorette) also marketed by the sponsor, and a single placebo-controlled clinical efficacy and safety trial. The sponsor intended to incorporate by reference the safety findings concerning Nicorette gum; however, the lozenge is not bioequivalent to the gum and delivers approximately 25% more nicotine than the analogous doses of Nicorette gum (also available in 2 mg and 4 mg strengths). Although the efficacy of the tested regimen was demonstrated, there is insufficient evidence of safety of the 4 mg lozenge to permit approval.

I. Recommendations

A. Recommendation on Approvability

Non-approval of this application is recommended due to insufficient evidence of safety in the intended population.

Additional safety data in a representative population of smokers, with typical concomitant illnesses found in the smoking population, should be generated using the 4 mg lozenge. Sufficient subjects should be enrolled to ensure that 200-300 subjects complete the full 6 weeks of treatment. It is understood that self-titration will occur and that exposure at the highest permitted dose cannot be ensured

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Not applicable.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The clinical program for the nicotine polacrilex lozenge consisted of 5 pharmacokinetic studies, an abuse liability study, a single placebo-controlled clinical efficacy trial, and a brief, open-label "usage" study best characterized as a market research study.

B. Efficacy

The efficacy of nicotine polacrilex lozenge was demonstrated in a single placebo-controlled clinical trial in which participants were randomized to treatment based on a measure of level of nicotine dependence. Participants were assigned to either 2 mg lozenge or 4 mg lozenge and self-titrated their use according to parameters provided in a simulated OTC label and user's guide. The full-dose treatment period was 6 weeks, followed by an additional 6 week tapering period and a 3 month period of occasional prn use. No concomitant behavioral support was provided.

Success was defined as self-reported abstinence from smoking from the end of week 2 to the end of week 6 (the last month of full-dose treatment), CO-verified at weeks 4 and 6. Additional analysis at the end of taper and end of study were performed (with CO verification at week 12 and month 6). Results are shown below.

	2 mg		4 mg	
Continuous Quit Rate (% abstinent continuously since week 2)	Active N = 459	Placebo N = 458	Active N = 450	Placebo N = 451
6 week	46%	30%	49%	21%
12 week	34%	22%	35%	14%
6 months	24%	14%	24%	10%

All comparisons to placebo were statistically significant.

The sponsor also evaluated the effect of nicotine polacrilex lozenge on various measures of craving and withdrawal relief. In the more dependent population (randomized to 4 mg lozenge on the basis of level of dependence), active lozenge was superior to placebo in reducing both craving and withdrawal. The less dependent population (2 mg group) had a mixed result, with statistical significance on withdrawal reduction depending on the analysis chosen. As this population is expected to have lower levels of withdrawal than the high-dependency group, this result is not unexpected. On measures of craving relief, nicotine polacrilex lozenge showed statistically significant superiority to placebo in the 2 mg group as well as the 4 mg group. The effects on both measures were transient in both groups, as would be expected given the transience of withdrawal symptoms after smoking cessation.

A single trial was considered adequate demonstration of efficacy because nicotine has proven superior to placebo in a variety of clinical studies encompassing different doses, dosage forms, routes of administration, and levels of concomitant behavioral support.

C. Safety

The safety of various forms of nicotine replacement therapy has been demonstrated in a variety of settings. Nicotine is available in transdermal and buccal (chewing gum) delivery systems over-the-counter and in nasal spray and oral/buccal "inhaler" for prescription use. The common adverse effects seen across studies include those associated with nicotine withdrawal or nicotine excess, and local effects specific to the dosage form (e.g. skin irritation for transdermal systems, mouth irritation and jaw problems for gum). The novelty of this product is that the 4 mg lozenge delivers plasma levels of nicotine higher than any other currently marketed NRT.

This renders the safety experience with other NRTs somewhat inapplicable in supporting the safety of the 4 mg lozenge.

C1. Adequacy of safety testing
Of a total population of 1818 subjects in pivotal study S1410043, 459 were randomized to receive the 2 mg lozenge and 450 were randomized to receive the 4 mg lozenge. Subjects reporting smoking at or after visit 4 (2 weeks) were discontinued; therefore attrition was high and the exposed population was ultimately significantly lower than the randomized population. In addition, concomitant smoking while using the product was likely uncommon as this led to study termination at the next visit.

Doses were self-titrated within parameters provided in the user's instructions. For the full-dose treatment period (maximum level of exposure, weeks 1-6), subjects were instructed to use one lozenge every one to two hours, with a range of 9-20 lozenges per day. Actual use was reported daily through a telephone call-in and the following table of exposure was requested from the sponsor.

Extent of Exposure to 2 mg Lozenge			
# Lozenges/Day	**N (%) of Subjects Reporting Level of use at Week 2 N = 347**	**N (%) of Subjects Reporting Level of use at Week 6 N = 206**	**N (%) of Subjects Reporting Level of use at Week 12 N = 144**
<1/day	18 (5%)	23 (11%)	40 (28%)
1-5/day	81 (23%)	61 (30%)	67 (47%)
6-10/day	173 (50%)	87 (42%)	32 (22%)
11-15/day	60 (17%)	32 (16%)	5 (4%)
16-20/day	15 (4%)	3 (2%)	0
>20/day	0	0	0

N's represent the number of subjects providing usage data that week.

Extent of Exposure to 4 mg Lozenge			
# Lozenges/Day	**N (%) of Subjects Reporting Level of use at Week 2 N = 358**	**N (%) of Subjects Reporting Level of use at Week 6 N = 225**	**N (%) of Subjects Reporting Level of use at Week 12 N = 177**
<1/day	5 (1%)	4 (2%)	14 (8%)
1-5/day	47 (13%)	39 (17%)	91 (51%)
6-10/day	178 (50%)	123 (55%)	54 (31%)
11-15/day	100 (28%)	37 (16%)	15 (9%)
16-20/day	27 (8%)	22 (10%)	3 (2%)
>20/day	1 (<1%)	0	0

N's represent the number of subjects providing usage data that week
From Dr. Blatt's Clinical Review and sponsor's data

The number of subjects completing the entire study (an additional three months of prn use, during which level of lozenge use was lower than in weeks 1-12) was 126 in the 2 mg (active lozenge) group and 118 in the 4 mg (active lozenge) group. Laboratory values and vital signs were not monitored; adverse events were collected during scheduled visits.

Because the product is self-titrated by the user, and nicotine's side effect profile is well-characterized, this extent of exposure, although low, is considered adequate to characterize the safety in the studied population. However, because subjects with cardiac disease were excluded, and because previous experience with NRTs cannot be relied upon to support the safety of the 4 mg tablet, this is insufficient safety data to predict the safety profile in the OTC market.

C2. Serious Adverse Events

No deaths occurred in subjects treated with active lozenge during the development program. The one SAE deemed related to drug treatment was a tracheal constriction caused by an allergic reaction in a subject in the 2mg active drug group. After discontinuation of the drug, the patient completely recovered without any further treatment.

C3. Common side effects

Although a checklist was not used, subjects were provided with a simulated OTC User's Guide which alerted subjects to the possibility of certain adverse events (mouth problems, nausea, vomiting, dizziness, diarrhea, weakness, and rapid heartbeat).

Most Common Treatment Emergent AEs (≥5%)
N (%) of ITT population reporting event

	2 mg		4 mg	
	Active n=459	**Placebo n=458**	**Active n=450**	**Placebo n=451**
Central and Peripheral Nervous System				
Headache	23 (5%)	27 (6%)	36 (8%)	15 (3%)
Gastrointestinal System				
Diarrhea	16 (4%)	10 (2%)	24 (5%)	17 (4%)
Flatulence	42 (9%)	33 (7%)	35 (8%)	23 (5%)
Heartburn	23 (5%)	10 (2%)	26 (6%)	4 (<1%)
Hiccup	15 (3%)	0	26 (6%)	0
Nausea	56 (12%)	22 (5%)	68 (15%)	24 (5%)
Respiratory system				
Coughing	19 (4%)	13 (3%)	25 (6%)	12 (3%)
Sore throat	12 (3%)	12 (3%)	23 (5%)	18 (4%)
URTI	55 (12%)	45 (10%)	44 (10%)	29 (6%)

C4. Drug-drug interactions

Drug-drug interactions involving nicotine have not been characterized. However, it has been noted that smoking cessation, with or without NRT, may change the metabolism of various drugs and may warrant dosage changes. Accordingly, OTC nicotine products carry a message that users of asthma medication (referring to theophylline) or medication for depression (refers to tricyclics) should notify their physicians of their quit attempt.

C5. Adequacy of exposure in trials versus probable marketing exposure
OTC nicotine replacement products are among the highest-selling drugs in the OTC category. Post-approval marketing is expected to be extensive and the exposed population large. Only approximately 900 subjects were exposed to active drug in the clinical trial program because the sponsor hoped to rely in part on the safety experience with Nicorette gum to support the application.

In this trial, subjects were instructed to use the product as often as hourly for the first 6 weeks and to taper over the subsequent 6 weeks. PRN use was permitted thereafter. Only 450 subjects received the active placebo at the 4 mg dose, and only 225 reported lozenge use at week 6, with 177 reporting use at week 12. The duration of exposure in actual use will also vary, as many people will discontinue use of the product if a quit attempt is not successful. The dose was self-titrated, and very few people used the highest permitted dose at any time point, suggesting that there is unlikely to be extensive use at above the tested dose.

While some consumers will use the OTC product indefinitely, the majority are likely to use the product within the duration tested. The duration of exposure, as well as the dose appear adequate but the total number of subjects exposed to the higher dose appears inadequate to establish the OTC safety profile of the 4 mg dose.

C6. Effect of trial exclusions on safety profile versus expected marketed population
Compounding the small size of the exposed population, the exclusion criteria generated a population not entirely representative of the general smoking population. Exclusions for cardiac disease eliminated the individuals at highest risk for adverse events related to nicotine's vascular effects.

C7. Relationship of safety to other drugs available for indication
Other drugs available for smoking cessation include various nicotine replacement products and bupropion. In nicotine-tolerant subjects (cigarette smokers), nicotine products are generally well-tolerated with the limiting adverse events generally associated with local irritation (e.g. cough/pharyngitis for inhaler, application site reaction for patch, tooth/jaw problems and GI upset for gum). The safety profile of the lozenge appears to encompass adverse events similar to those associated with nicotine gum. The self-titration affords some protection from symptoms of nicotine excess. However, titration is somewhat imprecise because of the delay between buccal absorption and CNS effects. The higher Cmax of the 4 mg lozenge (compared to 4 mg gum) is likely to yield a higher rate of symptoms of nicotine excess, although the two have not been directly compared.

C8. Abuse Liability

Abuse liability assessments were undertaken by the sponsor and reviewed by Dr. Cynthia McCormick....

C9. Additional safety data
Additional safety data submitted in support of this application was reviewed by Dr. Linda Hu...

C10. Unresolved safety issues
The safety profile of the 4 mg lozenge in a representative population of cigarette smokers remains to be established.

D. Dosing

For the products currently available over-the-counter, nicotine replacement therapy doses have been determined according to baseline smoking levels. Consumers who smoke less than 25 cigarettes per day are instructed to use the 2 mg Nicorette gum, while those who smoke more are instructed to use the 4 mg gum. Similarly, consumers smoking fewer than 10 cigarettes per day are instructed to use the "step 2" dose of Nicoderm or Habitrol (14 mg) vs the 21 mg "step 1 dose recommended for heavier smokers; or the 11 mg dose of the Elan patch (marketed under various private labels), while heavier smokers use the 22 mg patch. It may be noted that allocation to dose by baseline smoking rate does not appear to have been tested in placebo-controlled clinical trials for most products, and instead represents a "commonsense" recommendation. In fact, the Nicorette Rx label indicates that allocation to dose should be done according to level of dependence (although this, too, does not appear to have been tested), and several indices are suggested, including Fagerstrom score and smoking level.

In this application, the sponsors have chosen to use a simple measure of level of dependence: time to first cigarette of the morning (TTFC). This is an element of the Fagerstrom questionnaire, and the sponsor provided data showing an orderly relationship between Fagerstrom scores, TTFC, and smoking levels. The table below illustrates this concept, using two different cutoff points to define "lighter" smoking—the 25 cigarettes/day cutoff used in Nicorette labeling and the 20 cigarettes/day which represents the strong digit preference created by the packaging of cigarettes. The standard package contains 20 cigarettes and most smokers describe their smoking level in packs or fractions of packs.

	Low dependency by TTFC		High dependency by TTFC	
Baseline smoking level	**N**	**FTND Score Mean ± SD**	**N**	**FTND Score Mean ± SD**
<20 cpd	493	1.7 ± 1.39	128	4.4 ± 1.34
≥20 cpd	390	3.4 ± 1.44	771	6.5 ± 1.68
<25 cpd	756	2.1 ± 1.42	430	5.0 ± 1.40
≥25 cpd	127	4.5 ± 1.29	469	7.2 ± 1.39

Sponsor's Table 5.2.3

This data show that, as hoped, the FTND scores rise with level of dependency and smoking rate so that delayed TTFC, lighter smokers<delayed TTFC heavier smokers<early TTFC lighter smokers<early TTFC heavier smokers. This helps confirm the appropriateness of this simple, consumer-friendly self-assessment of level of dependence.

One safety concern raised by this method of dose allocation was that some lighter smokers, who would have been allocated to 2 mg lozenge using level of smoking as a criterion, would be assigned to the 4 mg dose because of an early TTFC. The sponsor addressed this concern through analysis of the safety experience of this subgroup, showing little difference between the lighter and heavier smokers assigned to the 4 mg dose.

Similarly, an efficacy concern raised by the TTFC method of allocation was that some heavier smokers, who would have been allocated to 4 mg lozenge using level of smoking as a criterion, would be assigned to a 2 mg dose because of a delayed TTFC. These subjects might be considered "undertreated." The sponsor addressed this concern through an efficacy analysis of this subgroup and found superiority to placebo in this group as well. These results are shown in the table below. All comparisons to placebo achieve statistical significance.

Quit Rates at Six Weeks by Baseline Smoking Level

	2 mg				4 mg			
	Active N = 459		Placebo N =458		Active N = 450		Placebo N = 451	
Overall	N	%	N	%	N	%	N	%
Success	211	61%	136	39%	219	70%	94	30%
Failure	248	44%	322	56%	231	39%	357	61%
<25 cpd	N = 385		N = 385		N = 226		N = 205	
Success	177	60%	119	40%	118	69%	54	31%
Failure	208	44%	266	56%	108	42%	151	58%
≥25 cpd	N = 74		N = 73		N = 224		N = 246	
Success	34	67%	17	33%	101	72%	40	28%
Failure	40	42%	56	58%	123	37%	206	63%

Table prepared using data from sponsor's tables 9.10.1.1.1; 9.13.1.1; and 9.14.1.1.

Thus, the doses tested in the clinical trial appear to have been effective and well-tolerated despite the potential for "mismatch" with respect to baseline smoking level.

The sponsor, however, proposes a different dosing regimen in the labeling. The clinical trial directions were to use 9-20 lozenges per day, one every 1-2 hours, not to exceed 5 lozenges in 6 hours. The proposed label calls for one lozenge every [redacted] -2 hours, at least [redacted] per day for the first six weeks, not to exceed [redacted] lozenges per day.

The PK studies show that the 4 mg lozenge delivers a plasma level of nicotine which exceeds that associated with the 4 mg Nicorette gum. In single-dose studies, the Cmax after 4 mg lozenge was 30% higher than after 4 mg gum. In multiple dose studies, "bioequivalence" was

demonstrated when the gum was dosed *hourly* and the lozenge was dosed *every 90 minutes*. The maximum dose of Nicorette 4 mg gum permitted in labeling is 20 pieces per day.

The proposed dose modification is a clear (although tacit) effort to ensure that the maximum total nicotine dose over the course of a day will be similar to that which a consumer using the maximum labeled dose of Nicorette 4 mg would experience, in the hope that this would allow the application to rest on the safety experience of Nicorette 4 mg despite the higher bioavailability of the 4 mg lozenge. Unfortunately, the efficacy of the product was demonstrated in a population using the product within the *tested parameters*. Although few subjects exceeded 15 lozenges per day, one cannot assume that the same distribution of use would be seen if the label [redacted] per day as the maximum, rather than 20. Consumers may be inclined to avoid using the maximum dose, and therefore some subjects who used 15 lozenges/day in response to labeling which permitted up to 20/day might well have used fewer. A resultant decline in efficacy would be predicted. There is no support for arbitrarily changing the dosing regimen from the one that was tested.

E. Special Populations

E1. Gender differences

Compared to male subjects, a slightly higher proportion of female subjects reported AEs at both 2 and 4mg doses. 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.

Women showed somewhat lower, but still superior to placebo, success rates in smoking cessation. The week 6 quit rate was 43% in women vs. 59% in men at the 2mg dose and 45% vs. 53% at the 4 mg dose.

E3. Ethnic/racial studies: differences in populations found, extent studied
E4. Issues with elderly, or patients with renal or hepatic impairment
E5. Status of pediatric studies and pediatric plan

E6. Pregnancy use information

The appropriate wording of the pregnancy warning on nicotine replacement products has been a subject of widespread discussion and litigation. There is significant private [redacted] and public (NICHD) interest in clarifying issues related to the use of NRT in pregnancy, and such research is underway. In this submission, the sponsor proposed the label language currently carried on the Nicorette and Nicoderm packages, which does not appear to adequately convey the appropriate message concerning the risks of NRT in pregnancy. A comprehensive review by the PTCC and the Division of Over-the-Counter Drug Products is aimed at developing appropriate "class labeling," and it is recommended that this product, once approved, carry the warning crafted through this effort.

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REVIEW AND EVALUATION OF CLINICAL DATA

NDA # 21-330

Sponsor: SmithKline Beecham Consumer Healthcare, L.P.
Generic Name: Nicotine Polacrilex Lozenge
Proprietary Name: Trade Name

Pharmacologic Class: 2030700

Proposed Indication: Reduction of Withdrawal Symptoms, Including Nicotine Craving, Associated With Quitting Smoking
Submission Date: December 14, 2000
Stamp Date: December 27, 2000
Dosage forms: Lozenge
Strengths: 2mg and 4mg

Route: Oral

Clinical Reviewer: Harold Blatt, D.D.S.
Statistical Reviewer: Stella Grosser, Ph.D.
Completion Date: May 23, 2001

EXECUTIVE SUMMARY

CLINICAL REVIEW

Executive Summary

1 RECOMMENDATIONS

1.1 Recommended Action

The safety and efficacy of nicotine polacrilex lozenge, 2 and 4 mg, has been demonstrated in this clinical trial. 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.

The benefits of smoking cessation include reductions in the incidence and prevalence of lung cancer, heart disease, stroke, and chronic obstruction pulmonary disease. Over-the-counter (OTC) marketing would make the lozenge available to large number of people interested in smoking cessation. The pivotal trial resulted in a statistically significant difference in quit rates of active drug over placebo at 6 weeks for both 2mg (46% vs. 30%) and 4mg (49% vs. 21%). The quit rates at 6months, while considerably lower than at 6 weeks, still showed a statistically significant difference of active drug vs. placebo for both 2mg (24% vs. 14%) and 4mg (24% vs. 10%) doses.

The most common adverse events (AEs) associated with nicotine replacement therapy (NRT) include nausea, heartburn, oral or throat related irritations including upper respiratory infections, headache, flatulence, hiccup, and diarrhea. However, it should be noted that the lozenge did not stick to dental work or cause the tooth or jaw disorders associated with nicotine gum. In general, cardiovascular risks include peripheral vasoconstriction, tachycardia, and elevated blood pressure. Despite this general concern, there were no substantiated cardiovascular AEs reported during the pivotal trial. 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. Various PK trials have shown safety at doses of up to 63 mg/day. Dosing at the proposed label recommended maximum of 15 lozenges/day would result in a total daily dose of 60 mg if 4mg lozenges were used. However, this differs from the tested regimen, which allowed for a maximum daily dose of 20 lozenges/day or 80 mg. The sponsor conducted an abuse liability trial and found that nicotine had significantly less abuse potential than amphetamine in both adult and young adult populations. The sponsor has stated that they plan to do [redacted]

[redacted] The sponsor has also stated their intent to [redacted]

[Item 3.I.1, pp.464-474.]

It appears to this reviewer that while there are some risks associated with the use of nicotine in NRT, they are outweighed by the potential benefits. The health risk from nicotine is not nearly as dangerous as the long-term exposure to tars and other carcinogens produced by a smoking tobacco product. It is this reviewer's opinion that, from a clinical perspective, the nicotine lozenge as an aid to smoking cessation should be approved provided the proposed marked up draft labeling is agreed to by the sponsor and the sponsor institutes and maintains their [redacted]

2 SUMMARY OF CLINICAL FINDINGS

2.1 Overview of Clinical Program

The sponsor submitted this NDA for Nicotine Polacrilex lozenge 2mg and 4mg as an aid to smoking cessation. The route of administration for the nicotine is absorption from the buccal mucosa with some additional amount of nicotine being swallowed. [Item 8.H.2., p. 293.] The sponsor submitted a total of seven trials. There were three single dose PK trials and one multiple-dose PK trial, one pivotal, randomized, double-blind placebo controlled parallel group, multi-center trial for safety and efficacy, a misuse trial to look at excessive or insufficient delivery of nicotine if the user did not follow the instructions, and an abuse liability trial.

In their pivotal trial, there was an ITT population of 1818 smokers divided into four groups of approximately 450 smokers per group. These groups were a 2mg active drug, a 2mg placebo, a 4mg active drug, and 4mg placebo.

2.2 Efficacy

The sponsor defined the primary efficacy variable as 28 days of continuous abstinence (smoking cessation) at the end of 6 weeks post-quit verified by an exhaled CO measurement of <10ppm. The sponsor also stated that this is a standard means of evaluating smoking cessation for nicotine replacement therapy (NRT) products. Note: This review examines outcomes both at 6 weeks and at the end of treatment (week 12). [Item 8.D.3, p.34.]

The study drug achieved a statistically significant difference in 6 week quit rates over the placebo of 46% vs. 30% for the 2mg dose and 49% vs. 21 % for the 4mg dose. For both the 2mg and 4mg doses, the p value was<0.0001. [Item 8.D.3., p.66.]

2.3 Safety

There were 179 subjects exposed to study drug in the clinical pharmacology studies, 24 in the abuse liability trial, and approximately 960 (459 at 2mg/450 at 4mg) in the pivotal trial for a total of 1163 subjects exposed to active study drug. These numbers include both 2 and 4mg doses. At 6 weeks post quit, 755 (397 at 2mg/358 at 4mg) subjects had received active drug. There were a total of 241 subjects who completed 6 months on study drug. [Items 3.H.3.e., and 3.H.4.e., pp. 445, 456.] There were no deaths or serious adverse events (SAEs) reported from the PK or abuse liability studies. However, three deaths were reported from the pivotal study. They all occurred in the 4mg-placebo group and are not related to the study drug. Among both strengths of active and placebo groups there were a total of 33 non-fatal serious SAEs. All except one were judged to be unlikely or unrelated to the study drug. The one case of significance was a tracheal constriction caused by an allergic reaction in a subject in the 2mg active drug group. After discontinuation of the drug, the patient completely recovered without any further treatment. [Item 8.H.1., p. 289.]

The most common AEs were nausea 12% in the 2mg group and 15% in the 4mg group (12%/15%), upper respiratory tract infection (12%/10%), flatulence (9%/8%), headache (5%/8%), heartburn (5%/6%), diarrhea (4%/5%) hiccup (3%/6%), coughing (4%/6%), and sore throat (3%/5%). [Item 3.H.4.e., pp.456-457.]

There is no information on drug-drug interaction potential because no such studies have been conducted with the nicotine lozenge. [Item 3.H.4.e., p. 459.]

The ratio of exposure to drug in these trials compared to the probable marketing exposure appears to be adequate. Patients were exposed to study drug with a possible duration of exposure of up to 24 weeks. [Item 3.H.2.c., p.438.] The label recommends using the study drug for up to 12 weeks. The ratio of exposure to drug in the trial compared to the probable marketing exposure appears to be adequate. The exclusion criteria used in the pivotal trial are mirrored in the "Warnings", "Directions" and "Other Information" sections of the proposed label. Therefore, it appears that the safety profile of the trial population should reflect that of the expected marketed population. [Item 3.A.1., pp.5-6, 7-9., and Item 8.D.2., pp.46-47.] It should also be noted that in the "Directions" section of the label there is a specific statement to completely stop smoking before beginning to use the lozenge. In general, nicotine replacement therapies (NRTs) are often associated with dyspepsia, nausea, diarrhea, hiccup, and hypertension. Nicotine overdose can result in vomiting, headache, dizziness, hypotension, tremor, mental confusion, and, in extreme cases, lead to respiratory failure or cardiac failure. It appears that the AE results recorded from the studies submitted with this NDA closely correlate with the general safety profile of NRTs.

2.4 Dosing

The sponsor based their dosing levels for both the 2mg and 4mg lozenges on the dose levels for the currently marketed gum. The recommended dosage in the trial was 9-20 lozenges/day for the weeks 1-6, a reduction down to 3-6 lozenges/day for weeks 10-12, and, if needed, a maintenance dose of 1-2 lozenges/day out to 6 months. The sponsor recommends all doses be discontinued at 6 months. [Item 8.D.3.4.5., p.25.]

The sponsor notes that their clinical development program did not include any formal dose response studies and did not compare the 2mg dose in low dependency smokers with the 4-mg dose in high dependency smokers. There does not appear to be an AE dose response relationship in either the 2mg or 4mg doses. The higher incidence of gastrointestinal problems, headache, and coughing in the 4mg group may be a result of smoking cessation and their greater dependence on nicotine. [Item 8.H.1.13, p. 290.]

The dosing in the trial as described in the first paragraph of this section varies slightly from the dosing in the proposed label, and also from labeling for the approved gum. The sponsor decided to change the dosing in proposed label from the dosing that was done in the trial as follows: the label recommendation is for [redacted] /day for weeks 1-6 (vs. 9-20 lozenges/day in the trial), and to discontinue use of the lozenge at 12 weeks (vs. continuing a dose of 1-2 lozenges/day for up to 6 months if needed to stay smoke-free). The gum has a recommended dosage of 12-24 pieces/day for weeks 1-6, and discontinuation at 12 weeks. One of the reasons the sponsor gives for labeling at a maximum of [redacted] lozenges/day was that current labeling in Germany and Ireland already state that maximum limit. To resolve this discrepancy the sponsor performed efficacy and safety analyses of those subjects who used 15 lozenges/day or less. The result shows a success rate at 6 weeks of 44% for the 2mg dose (176 subjects vs. 211 overall) and 47% for the 4mg dose (167 subjects vs. 219 overall). Both doses showed statistically significant differences from placebo with a p value of <0.0001. For safety, at 6 weeks the treatment emergent AEs at were comparable for the 2mg groups but at 4mg those taking >15 lozenges/day showed a higher incidence of treatment emergent AEs. [Item 8.D.5.1.13. and Item 8.D.6.2.2.6, pp.81, 101-102.]

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 (depression, insomnia, sleep disturbed, viral infection, and coughing), this may be a result of these subjects being more highly addicted and not a function of the increased use of the lozenge. Since we have no statistical method for determining how many lozenges subjects will take if instructed to take a maximum of 15/day, the lozenge is to be used for a limited amount of time, and is considerably safer than smoking a cigarette, this reviewer is of 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 for the first 6 weeks and continuing a dose of 1-2 lozenges/day for up to 6 months if needed to stay smoke-free.

Special Populations

The proposed draft label states that the special populations such as women who are pregnant or breast-feeding or anyone with cardiovascular disease contact their physician or health professional before using this product.

More women than men reported AEs in at both 2 and 4mg doses. Women showed a success rate of 43% vs. 59% in men at the 2mg dose and 45% vs. 53% at the 4 mg dose.

At 6 weeks Caucasians reported AEs in the same ratio as the overall ITT population. Blacks and Asians reported lower AEs at the 2mg dose but higher AEs at the 4mg dose than the overall ITT population. Caucasians showed a success rate of 46% vs. 52% in Blacks, and 40% in Asians at the 2mg dose, and 49% vs. 40% in Blacks at the 4mg dose. Only 2 Asians were in the active drug 4mg group and they both failed at smoking cessation.

At 6 weeks, among the nicotine exposed subjects, those over $\geq$ 55 reported a higher incidence (73%) of treatment-emergent AEs than all ages combined (68%) at the 2mg dose, and 75% for those $\geq$ 55 vs. 71% for all ages at the 4mg dose. But the type of AEs was the same for both groups. Those subjects under 55 showed a success rate of 46% at 2mg and 45% at 4mg. Those over 55 showed a success rate of 44% at 2mg and 64% at 4mg. [Item 8.H.15.3, pp. 352-358 an Item 8.D.8, Tables 9.11.1, 9.11.2, and 9.11.3, pp. 474-476.].]

In the application, the sponsor requested a deferral for the submission of data on the safety and efficacy of their lozenge on the pediatric population because they did not feel their data would be available before the December 2, 2000 compliance date. However, they have initiated PK study on 4 NRT formulations in adolescent smokers. It is a single-dose, open-label, dose escalation study in 48 subjects aged 10-17 who smoke >10 cigarettes/day. They noted that data on the pediatric population should only be used in labeling information for the physician and is inappropriate for OTC labeling.

Clinical Review

1 INTRODUCTION AND BACKGROUND

The sponsor has developed the nicotine lozenge as an alternative to nicotine gum. It has been observed that some individuals do not like chewing, find that the gum can stick to dental work, or that chewing can precipitate temporomandibular joint problems (pain, open or closed "locked" jaw, limitation of opening). The rationale for this new form is to help more smokers to quit by providing a more acceptable and easily used form of nicotine aid for smoking cessation. It should be noted that the drug substance and nicotine delivery profile of the lozenge is similar to the gum. The potential health benefits of quitting include reduction in the risk of developing lung cancer, heart disease, stroke, and chronic pulmonary obstruction disease.

1.1 Proposed Indications

This product is to be used as an aid in smoking cessation. The proposed label gives the indication as , "reduces — withdrawal symptoms including nicotine craving associated with quitting smoking."

1.2 Foreign Marketing

According to the sponsor there are several distributors of a nicotine lozenge for NRT in 10 countries. Nicotine gum is distributed in 21 countries. The sponsor also states that, to their knowledge, no nicotine lozenge or gum has ever been removed from the market for reasons of safety. [Item 3.C., pp. 56-57.]

2. Chemistry

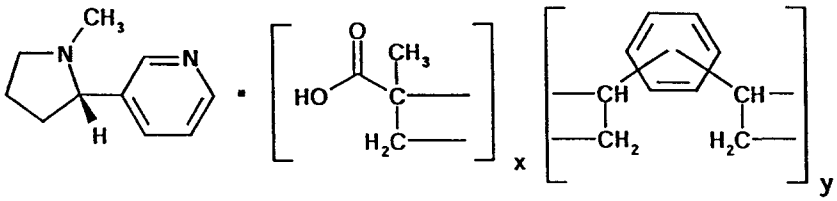
DRUG:

Trade Name: Nicotine Polacrilex Lozenges, 2 mg and 4 mg

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

CAS Registry Number: 96055-45-7

Structure (from Sponsor):



Empirical formula: $C_{10}H_{14}N_2(C_4H_6O_2)_x(C_{10}H_{10})_y$

Relative molecular mass: [redacted]

where: x = number of [redacted] units per NPA molecule
y = number of [redacted] units per NPA molecule

RELATED INDs/NDAs/DMFs: IND 56,295; DMF [redacted] DMF [redacted]

PHARMACOLOGIC CLASS: Nicotinic cholinergic receptor agonist

PROPOSED CLINICAL INDICATION: Reduction of withdrawal symptoms, including nicotine craving associated with quitting smoking

FORMULATION (Sponsor's Table):

Table 4.A.2.b-1
Quantitative Composition of Nicotine Polacrilex Lozenges

Ingredient Name	Composition (mg/lozenge)	
	2 mg lozenge	4 mg lozenge
Nicotine Polacrilex, USP[1]	[redacted]	[redacted]
Mannitol, USP[2]	[redacted]	[redacted]
Sodium Alginate, NF[2]	[redacted]	[redacted]
Xanthan Gum, NF[2]	[redacted]	[redacted]
Potassium Bicarbonate, USP[2]	[redacted]	[redacted]
Calcium Polycarbophil, USP[2]	[redacted]	[redacted]
Sodium Carbonate, NF[2]	[redacted]	[redacted]
Aspartame, NF	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Magnesium Stearate NF	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Total lozenge weight	1200.000	1200.000

[1] Amount of Nicotine Polacrilex, USP will vary depending upon the potency (nominally 18% w/w nicotine).

[2] Amount of these ingredients (added as Mannitol [redacted]) is adjusted dependent on the calculated quantity of Nicotine Polacrilex, USP used.

[3] Used as a [redacted] and evaporates during the [redacted]

Please see Chemistry review for a more detailed discussion of chemistry issues.

3 Pharmacotoxicology

The Pharm/Tox reviewer has noted that the sponsor is requesting a direct-to-OTC switch.
No animal studies have been conducted with the Nicotine Polacrilex Lozenge. However, the active ingredient, nicotine polacrilex, has been studied under IND #17,689 (Nicotine Polacrilex Gum), NDA #18-612 (2 mg Nicotine Polacrilex Gum), and NDA #20-666 (4 mg Nicotine Polacrilex Gum).

The basic pharmacology and toxicology of nicotine was reviewed and summarized by the sponsor from published literature reports. The following is a condensation of the Pharm/Tox Reviewer's summary of nicotine that was, in turn, based on the sponsor's summary. Please see the Pharm/Tox review for a more complete discussion and a list of references.

"The general pharmacology, pharmacokinetic and toxicology profile of nicotine in animals has been largely superseded by the extensive human experience with this agent. The principal metabolites of nicotine, as well as the degradation products identified in Nicotine Polacrilex Lozenges, ——— ——— and ——— show little pharmacological activity and have not been demonstrated to produce toxic effects.

"There are safety concerns regarding neonatal exposure to nicotine in humans. For this reason, the advice regarding use of Nicotine Polacrilex Lozenges during pregnancy and lactation described in the product labeling is considered by the sponsor to be appropriate, in that use by pregnant women should be subject to a risk benefit assessment by a physician. However, class labeling for OTC nicotine products is currently under review advising women that nicotine, although not as harmful as cigarette smoking, may not be without risk to a developing fetus.

"Evaluation of the mutagenic potential of a range of nicotine concentrations in a variety of *in vitro* and *in vivo* mutagenicity tests has shown that nicotine was not mutagenic in appropriate assays. The majority of evidence also indicates that nicotine and its primary metabolite, cotinine, are not carcinogenic. Although, the results of several studies indicate that nicotine and nicotine N-oxide may, under certain conditions, possess a cofactor or co-carcinogenic potential. Additionally, although it has been shown that TSNA occur in tobacco products containing nicotine and related secondary amines, there is no clear evidence that such compounds are formed *in vivo* in humans from use of nicotine replacement therapy products.

"No significant effects on the oral mucosa are anticipated with use of Nicotine Polacrilex Lozenges. Use of a similar product containing nicotine was shown to be well tolerated in humans over a 3 to 6 month period of use, and pre-clinical studies have demonstrated that oral application of nicotine for periods up to 13 months had no apparent adverse effect on the oral mucosa.

"Nicotine Polacrilex Lozenges appear to be safe from a toxicological perspective for the proposed indication. However, the use of Nicotine Polacrilex Lozenges during pregnancy may not be without risk. Specific labeling for this and other OTC nicotine replacement products is warranted, and is currently under review by the Office of Over-The-Counter Drugs.

LABELING (Package Insert):

"Because of animal studies showing nicotine-induced alterations during fetal brain development, the following labeling proposed by the sponsor is currently under review by the Office of Over-The-Counter Drugs:

"

4 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

The PK Reviewer has summarized the 5 human PK trials as follows:

"Initially, two pilot, single dose studies were conducted comparing NPA lozenge with Nicorette ®: gum at 2 and 4-mg dose levels (Studies N98001 and N96016). Based on the findings from these early development studies, the applicant has conducted additional PK studies: (1) Bioequivalence study comparing 3 mg NPA lozenge and 4 mg Nicorette® gum (Study S1410092). (2) Multiple dose study applying different dosing regimens to NPA lozenge and Nicorette® gum (Study S 1410091). (3) A study to compare the extent of absorption when the lozenge was administered as directed and not as directed (Study S1410090). Additionally, a simulation was carried out to predict the extent of absorption when the lozenge was administered every 60 minutes (as opposed to q. 90 min in S1410091). Overall PK of NPA lozenges can be adequately characterized from the 5-PK studies conducted by the sponsor."

The only PK concern is that the sponsor needs to resubmit the dissolution method/specification to more accurately reflect the dissolution in vivo.

Please see the PK review for a more detailed discussion.

5 REVIEW METHODS

5.1 Evaluation of Data Quality and Integrity

On February 20, 2001, at Administrative Rounds it was decided that no DSI investigation of the trial site would be performed unless some new information was to come to light in the course of the review process that would require such an investigation. This reviewer examined the derived efficacy data dataset in JMP regarding the 6-week success rate for 2mg and 4mg doses. I compared this data to the sponsor's tables and Summary results. No discrepancies in success rates were found. [Item 3.H.3.a, p.441, and Item 11, Derived Datasets for study S1410043, Derived Efficacy Data (EFFICT).]

In study S1410043 there were three reports of patient deaths all of which occurred in the 4mg-placebo group and none of which considered to be related to treatment. One patient died of a myocardial infarction, one of a brain aneurysm, and of a ruptures aortic bypass graft. [Item 8.H.7.2.2.1, p.346.] There were also a total of 33 serious adverse events (SAEs). This reviewer examined the line listings to the sponsor's table. No discrepancies were found. [Item 8.H.7.2.2.2, pp.345-346, and Item 11, Derived AE Dataset for study S1410043]

There were 5 discontinuations due to AEs in the clinical pharmacology studies and 64 in the 2mg (31) and 4mg (33) nicotine groups. The most frequent reasons for discontinuation were nausea, mouth soreness, diarrhea, flatulence, and heartburn. Only one AE of severe symptoms including chest pain, gas, and heartburn was considered clinically significant and related to study drug. This reviewer examined this subject's CRF and found that her pain was not relieved by [redacted] was referred back to her physician who sent her for a GI series. [Item 8.H.3.1.8, p. 289, and CRF 90043, pp.12, 14.] This reviewer examined the line listings from the Derived Adverse Event Dataset for study S1410043, and looked for discontinued patients especially those in the 4mg-nicotine dose group (the 2mg dose is more widely documented). My survey found AEs that appeared to be of minor clinical significance and generally corresponded to the results the sponsor's mentioned in the text of their submission.

5.2 Financial Disclosure

In Item 19 of this submission, the sponsor provided a list of covered clinical studies, a list of Investigators from the "covered clinical studies, and "Certification: Financial Interests and Arrangements of Clinical Investigators Form 3454.These information certifies that the sponsor has not entered into a financial arrangement with the investigator that is dependent on the outcome of the study. Also, that the investigator has not disclosed any proprietary interest in the product or equity in the sponsor's company. These statements appear to satisfy the financial disclosure requirements.

It should be noted that the sponsor made the following special exceptions:

- The Label Comprehension Study 2117 was not used to assess safety or efficacy and did not meet the requirements of a "covered clinical study." Therefore it was not subject to the rules of financial certification and disclosure and was not included.
- [redacted] in Study S1410089 has an on-going consultation agreement with the sponsor. He was involved in protocol design but not directly involved in the treatment or evaluation of subjects in this trial. [Item 19, pp.1-27.]

6 DESCRIPTION OF DATA SOURCES

6.1 Overall Data

The sponsor submitted this NDA for Nicotine Polacrilex lozenge 2mg and 4mg as an aid to smoking cessation. The route of administration for the nicotine is absorption from the buccal mucosa with some additional amount of nicotine being swallowed. [Item 8.H.2., p. 293.]

The submission only contains primary source data. The sponsor submitted a total of six trials that will be reviewed by this Division. Of these 5 were PK studies that will be reviewed in detail in a separate PK review. The data from these clinical pharmacology trials were included in the Integrated Summary of Safety. All PK studies were single-center, randomized, open label, crossover studies:

- 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 4mg gum at steady state (S1410091),

- A single dose, PK misuse trial to look at excessive or insufficient delivery of nicotine if the user did not follow the instructions (S141090),
- One pivotal, randomized, double-blind placebo controlled parallel group, multi-center trial for safety and efficacy (S140043),

In their pivotal trial (S140043), there was an ITT population of 1818 smokers divided into four groups of approximately 450 smokers per group. These groups were a 2mg active drug, a 2mg placebo, a 4mg active drug, and 4mg placebo. From the 5 clinical pharmacology (PK) studies there were 179 subjects evaluated for safety. In the abuse liability study (S1410089) there were 24 subjects.

See Reviewer's Table 1 on next page:

Reviewer's Table 1

Trial Number	Type of Trial	Number of Subjects

S1410092	Bioequivalence, open-label, randomized, single-dose, two-way crossover comparing 3mg lozenge and 4mg gum	79 (47m/32f)
N98001	PK, open-label, randomized, single-dose, two-way crossover comparing 2mg lozenge and 2mg gum	25 (12m/13f)
N96016	PK, open-label, randomized, single-dose, four-way crossover and replicate design comparing 4mg lozenge and 4mg gum	20 (10m/10f)
S1410091	PK and bioavailability, open-label, randomized, multiple-dose, four-way crossover comparing 2mg and 4mg lozenges and gum at steady state.	33 (15m/18f)
S1410090	Misuse trial. PK, open-label, randomized, single-dose, three-way crossover comparing 4mg lozenge used as directed, chewed and immediately swallowed, and chewed, retained in mouth for 5 minutes and then swallowed.	22 (11m/11f)
S1410043	Randomized, multicenter, double-blind, placebo-controlled, parallel group study examining efficacy in 2mg and 4mg lozenges	1818 (788m/1030f)

[Based on sponsor's tables Item 6, Table 6.A.1, pp. 2-3, Item 8.D.3, Table 5.2.1, p. 59, and Item 8.H.1.2, p.285.]

In addition to the clinical 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, a study of teen reactions and impressions of concept presentations, and two labeling comprehension studies. The Division of Over-the-Counter Drugs (HFD-560) will review these studies.

The Controlled Substance Staff will review the abuse liability study S1410089 that is a single-center, randomized, double-blind, placebo-controlled trial). See Table 2 below.

Reviewer's Table 2

S1410089	Abuse liability, single-center, randomized, double-blind, placebo-controlled, 8 way crossover study comparing 2,3,4, and 8mg lozenges. Assessment made using d-amphetamine, 4mg gum, two confectionery lozenges and placebo. Note: This trial not included in safety evaluation.	24 (14m/10f)

[Based on sponsor's table Item 6, Table 6.A.1, pp. 2-3]

The demographic characteristics of the subjects in the pivotal trial showed roughly equal number in all 4 arms, with similar mean ages, age ranges, and weights. There were consistently more women than men in all four groups. The majority of subjects were Caucasian with much smaller numbers of Blacks, Asians, and others. See Reviewer's Table 3 below:

Reviewer's Table 3

	2mg nicotine n=459	2mg placebo n=458	4mg nicotine n=450	4mg placebo n=451	Total Population n=1818
Age (years)					
Mean	41.1	40.5	44.3	44.5	42.6
Ranges	18.9-77.7	18.3-76.9	19.0-76.4	18.1-73.4	18.1-77.7
Weight (kg)					
Mean	75.61	74.56	77.99	75.72	75.96
Sex					
Male	197	184	195	212	788
Female	262	274	255	239	1030
Race					
Caucasian	426	428	421	432	1707
Black	21	16	15	8	60
Asian	5	6	2	1	14
Other	7	8	12	10	37

[Based on sponsor's Item 8.D.3, Table 5.2.1, p.59.]

The number of men and women in the clinical pharmacology trials was roughly equal except in study S1410092 where there were 47 men and 32 women. Caucasians made up the largest racial group in these studies (86.6%). The mean age was 30 in three of the studies and 34 in the other two studies. In the abuse liability study 18 or 75% were Caucasian, 6 or 25% were non-Caucasian and the average age of the subjects was 30 years. [Item 8.H.1.2, p.285.]

In the pivotal study S1410043, the average daily exposure to drug at week 6 was 6.3 lozenges or 12.6mg of nicotine for the 2mg nicotine lozenge group (206 patients) and 8.6 lozenges or 34.4mg of nicotine for the 4mg nicotine lozenge group (225 patients). The greatest daily exposure to drug was at week two for both the 2mg and 4mg doses. This reviewer examined the Table 4.2.1 and compared the results with Table 9.2.1.1. No discrepancies were found.

Reviewer's Table 4

Number of Lozenges		
Dose	**Week 2**	**Week 6**
2mg nicotine	**7.4 (range 0-20)**	**6.3 9 (range 0-16.9)**

(n=459 at randomization)	(n=347)	(n=206)
No. (%) of Subjects Using <1/day	18 (5%)	23 (11%)
No. (%) of Subjects Using 1-5/day	81 (23%)	61 (30%)
No. (%) of Subjects Using 6-10/day	173 (50%)	87 (42%)
No. (%) of Subjects Using 11-15/day	60 (17%)	32 (16%)
No. (%) of Subjects Using 16-20/day	15 (4%)	3 (2%)
No. (%) of Subjects Using >20/day	0	0
4mg nicotine (n=451 at randomization)	**9.1 (range 0-21) (n=358)**	**8.6 (range 0-20) (n=225)**
No. (%) of Subjects Using <1/day	5 (1%)	4 (2%)
No. (%) of Subjects Using 1-5/day	47 (13%)	39 (17%)
No. (%) of Subjects Using 6-10/day	178 (50%)	123 (55%)
No. (%) of Subjects Using 11-15/day	100 (28%)	37 (16%)
No. (%) of Subjects Using 16-20/day	27 (8%)	22 (10%)
No. (%) of Subjects Using >20/day	1 (<1%)	0

[Based on sponsor's Table 4.2.1, Item 8.H.4.0, p.312, and Table 9.2.1.1, pp. 138-143, and June 6, 2001 General Correspondence.]

Of the clinical pharmacology trials, Study S1410090 exposed 20 subjects to the 4mg Lozenge three times for a total exposure of 12mg. Study S1410091 had 26 subjects exposed to 9 doses of the 2mg and 4mg lozenge. The average dissolution time was 15.7 minutes for the 2mg dose and 17.3 minutes for the 4mg dose. Study 1410092 had 65 subjects exposed to a single dose of 3mg lozenge. The average dissolution time was 23.6 minutes. Study N96016 had 14 subjects receiving of 4mg lozenge over a thirty-minute period. Study N98001 had 23 subjects exposed to 2mg lozenge over a thirty-minute period. The average dissolution time was 20.8 minutes with a maximum time of ——
See tabular representation below:

Reviewer's Table 5

Trial Number	Number of Subjects Exposed to Nicotine Lozenge	Amount or Duration of Exposure of Nicotine Lozenge	Mean Dissolution time
S1410090	20	4mg three times or 12mg	
	26	2mg and 4mg for 9 doses.	15.7 minutes for 2mg

S1410091			17.3 minutes for 4mg
S1410092	65	3mg single dose	23.6 minutes
N96016	14	4mg single dose	30 minutes
N98001	23	2mg single dose	30 minutes

[Based on Item 4.0, p.310-311.]

7 REVIEW OF EFFICACY

7.1 Individual Review of Studies

Study S1410043:

Findings vs. Labeling Claims

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 withdrawal symptoms. See section on Secondary Efficacy Variables.

Population, Design, and Objectives

This was a randomized, double-blind, placebo-controlled, parallel group, multicenter study at 15 sites. Lozenge strengths of 2mg and 4mg were studied in smokers with high and low levels of nicotine dependence.

Inclusion criteria

1. Subject had to be 18 years of age or older.
2. Subject had to be interested in smoking cessation within 30 days using nicotine lozenges.
3. Subject was able to read and understand English and capable of providing written informed consent.

Exclusion criteria

1. Subject who used other forms of tobacco other than cigarettes such as pipes, cigars, snuff, or smokeless tobacco within 30 days of entry into the study.

2. Subject who used other nicotine delivery system such as nicotine gum, nicotine patch, nicotine inhaler, or nicotine nasal spray etc. within 30 days of study entry,
3. Subject who smoked any other substance within 30 days of study entry.
4. Subject who used other smoking cessation aids (including bupropion, herbals, counseling, etc.) within 30 days of study entry.
5. Subject who was currently involved in another clinical trial or had used any

investigational drug within 30 days of study entry.
6. Subject who was a member of the same household as another clinical subject or a relative of study site staff or a member of the study staff.
7. Subject who was pregnant or lactating, or planned to become pregnant within 6 months.
8. Subjects who had diagnosed heart disease being treated with medication or had an irregular heartbeat or had a heart attack within the last 3 months.
9. Subjects with diagnosed stomach ulcers
10. Subjects with high blood pressure not controlled by medication.
11. Subjects who were taking insulin for diabetes
12. Subjects who were unable to fulfill study requirements in relation to conforming to the visit schedule
13. Inability to metabolize aspartame or phenylalanine (added as protocol amendment)

Subjects who had a genetic deficiency with inability to metabolize aspartame or phenylalanine, or had been diagnosed with phenylketonuria (PKU). [Taken from Item 8.D.3.3.1, pp.21-22.]

In their pivotal trial (S140043), there was an ITT population of 1818 smokers divided into four groups. These groups were a 2mg active drug (n=459), a 2mg placebo (n=458), a 4mg active drug (n=450), and 4mg placebo (n=451).

The objective of this study was to evaluate the safety and efficacy of the 2mg and 4mg doses of lozenges for smoking cessation as measured by continuous abstinence for a 28-day period. The abstinence was verified by carbon monoxide at 6 weeks post-quit.

Treatment Summary

The initial treatment plan called for a planned enrollment of 1688 smokers who were desired to quit. These 1688 were to be divided into four groups of 422 each. Participants were to report to the study site at enrollment one week before quit date, quit date (week 0), 1, 2, 4, 6, and 12 weeks, and 6 and 12 months for post-quit assessments. Quit date (week 0) was when randomization was done based on degree of nicotine dependence or time to first cigarette. The first question on the Fagerstrom Nicotine Dependence Questionnaire ("How soon after you wake up do you smoke your first cigarette?") was used to determine the degree of dependency (high or low). Those who reported they took their first cigarette in 30 minutes or less after waking were randomized to receive the 4mg dose or placebo (high dependency group) and those who reported 31 minutes or longer were randomized to the 2mg dose or placebo (low dependency group). What the sponsor referred to as "low intensity behavioral support" was provided to smokers by giving them a copy of the User Guide at each visit and directing their attention to the behavioral treatment information. This "low intensity behavioral support" was provided at the enrollment visit, quit date visit (week 0), and visits at weeks 1, 2, and 4. Staff was instructed not to give instructions beyond those in the User Guide. [Item 8.D.3.1, p.19.]

An advertisement was used initially recruit subjects. Potential subjects were asked to indicate their interest in participating by calling a specific telephone number. During that initial call potential subjects called were questioned as to their interest in quitting, when they took their first cigarette after waking, and if they met the study entry criteria. Those who met the criteria were given information about

number and time of study visits, procedures, and potential study treatments and a first visit appointment was scheduled. At the first appointment Informed Consent was agreed to and signed and subjects were told their quit date would be for their second visit in one week. Carbon monoxide (CO) measurements were made using a ———————— with results recorded in the CRF. CO measurements were made at all visits and was used to determine if a subject could remain in the trial. Determination of abstinence was begun on visit 4 (2weeks). Any subject who had a CO level of >10ppm on visit 4 (2 weeks) was considered a failure and was discontinued. Any subject who, after visit 4, reported smoking or showed a CO level >10ppm was also considered a treatment failure and discontinued.

Subjects daily reported their craving and withdrawal symptoms via a telephone Interactive Voice Response System (IVRS) from enrollment to week 6. Daily use of lozenges was also recorded throughout the study by the IVRS.

AEs, concomitant medications and body weight were recorded at study visits after baseline. [Item 8.D.3.1, pp. 17-19, 28.]

Subjects were directed to take 1 lozenge every one to 2 hours up and from **9-20 lozenges/day** for the first 6 weeks. They were then recommended to taper down over the next 6 weeks to arrive at between 3-6 lozenges/day during weeks 10-12. To prevent relapse they were to take 1-2 lozenges/day out to 6 months. The User's Guide gave the following instructions:

- "Place the lozenge in your mouth and allow the lozenge to dissolve.
- Do not chew or swallow the lozenge.
- Periodically move the lozenge to the other side of your mouth.

Repeat this process until the lozenge is completely dissolved.

- Use according to the recommended schedule below for the first 12 weeks of treatment.

Reviewer's Table 6

Weeks 1-6	**Weeks 7-9**	**Weeks 10-12**
1 lozenge every 1 to 2 hours; do not exceed 5 lozenges in 6 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4-8 hours

[Copy of sponsor's Table Item 8.D.3.4.5, p.25.]

- To remain smoke free after the first 12-week treatment period, keep the lozenges available and use occasionally in situations where you may be tempted to smoke.
- Discontinue the use of the lozenge at the end of 6 months.
- Do not exceed 20 lozenges per day." [Item 8.D.3.4.5, p.25.]

Assessments

The primary endpoint for efficacy was smoking cessation at six weeks post-quit. The cessation was indicated by continuous abstinence for 28 days as verified by a carbon monoxide (CO) level of <10-ppm. Smoking cessation assessments were also made at three and six month post-quit.

Safety was assessed by adverse events (AEs) reported during the study.

Analysis Plan

The smoking cessation rate was compared using the Chi-square test at 6 weeks, 3months, and 6 months. To evaluate the differences in total withdrawal and craving between active and placebo groups in weeks 1 and 2 an ANCOVA was done. The Wilcoxon rank sum test was used where the data was non-parametric. All analyses were done on ITT and Per-Protocol populations. [Item 8.D.2, p.48.]

Study Conduct

All protocol deviations were included in the ITT analysis but not in the per protocol analysis. Most protocol deviations were subjects who did not to come to visits at the appropriate date and time (437) or completely missed visits (65). Twenty-six subjects never came for some visits and also came at the wrong time for other visits and were therefore included twice in the protocol deviations. Sixty subjects took no study medication. Three subjects (5562, 5564, and 5569) at site 87 violated inclusion/exclusion criteria because they had heart disease, and one at site 83 (5659) had a stomach ulcer. Five subjects had taken Wellbutrin (83062, 82130, 82056, 91062, and 91051), three (31157, 31155, and 90043) has used nicotine gum, and three 91065, 32120, and 32216) had used nicotine patches. Thirty-four subjects were put in the wrong treatment group. This came to a total of 611 that were excluded from the per-protocol analysis.

Reviewer's Table 7 Reasons for exclusion from per-protocol analysis

	Frequency
Patient attended outside visit window	437
Subject did not attend a scheduled visit	65
Subject did not take any study medication	60
Subject found to have violation of exclusion criteria after randomized	4
Subject took prohibited medication	11
Subject was allocated to wrong dependency group	34
Total	611

[Based on Sponsor's Table 4.2, Item 8.D.3.4.2, pp.56-57.]

It should be noted that the 11 subjects who took prohibited medication should not have included in the ITT analysis. However, the calculated quit rate does not change appreciably (a difference of >1%) if the successes among those who took the prohibited medication are removed from the ITT analysis.

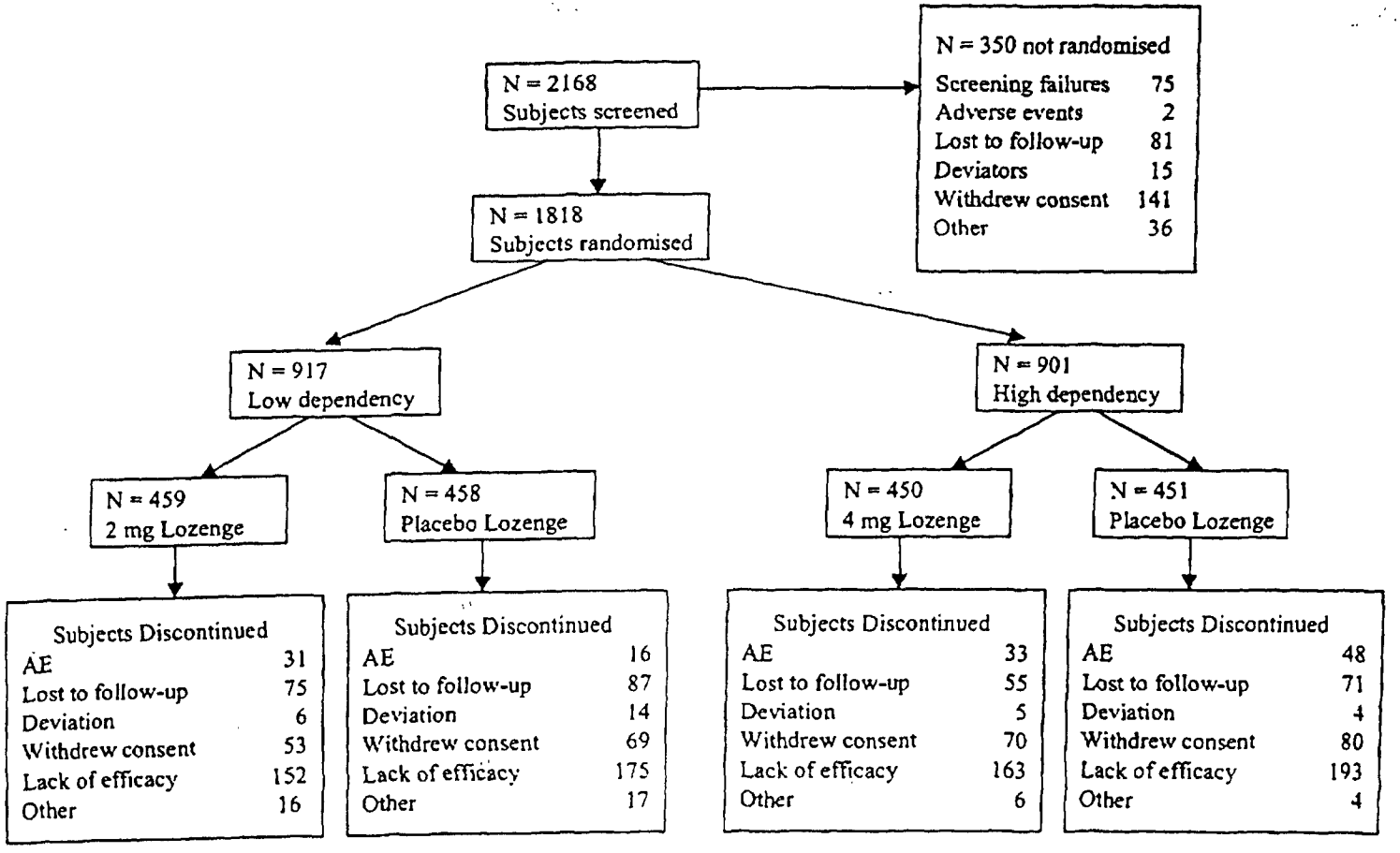
This reviewer examined the data from the derived dataset for protocol deviations (PROTDEV.XPT) and compared the results to the numbers in Table 4.2 above. No deviations were noted.

Patient Disposition

Out of the 2168 subjects who actually attended the first screening visit, 1818 were randomized and became the ITT population. There were 350 not randomized. In the ITT population 917 were low dependency smokers (459 got 2mg study drug /458 got placebo, and 901 were high dependency smokers 450 got 4mg study drug/451 got placebo). This reviewer calculates that only 376 actually finished the trial. See next page for a copy of sponsor schematic (Reviewer's Table 8) for subject disposition:

[Copy of sponsor's Figure 4.1, Item 4.1, p. 55.]

ure 4.1: Subject Disposition



Demographics/Group Comparability

Reviewer's Table 9

	2mg NICOTINE n=459	2 mg PLACEBO n=458	4 mg NICOTINE n=450	4mg PLACEBO n=451	TOTAL (ITT) n=1818
AGE					
Mean	41.11	40.48	44.28	44.51	42.58
Range	18-9-77.7	18.3-76.9	19.0-76.4	18.1-73.4	18.1-77.7
SEX					
Male	197 (43%)	184 (40%)	195 (43%)	212 (47%)	788 (43%)
Female	262 (57%)	274 (60%)	255 (57%)	239 (53%)	1030 (57%)
RACE					
Caucasian	426 (93%)	428 (94%)	421 (94%)	432 (96%)	1707 (94%)
Black	21 (5%)	16 (4%)	15 (3%)	8 (2%)	60 (3%)
Asian	5 (1%)	6 (1%)	2 (0.4%)	1 (0.2%)	14 (0.8%)
Other	7 (2%)	8 (2%)	12 (3%)	10 (2%)	37 (2%)

[Based on sponsor's Table 5.2.1, p. 59.]

The above table shows that demographically, there was little difference between groups at the time of study entry. This reviewer compared the data in the Table above with the sponsor's Table 9.4.2.1 [pp.268-271.] and found no discrepancies.

Unplanned Analyses

There were changes in the conduct of the study in the form of two formal protocol amendments.

Protocol amendment 1 in July, 1999, noted the omission of an exclusion criterion. Since both doses of lozenge contained aspartame, subjects with PKU should be excluded from the trial. Appropriate changes were made to the CRFs.

Protocol amendment 2 dated February 4, 2000, noted that if no differences could be detected by post-quit week 6, the trial would be stopped so subjects could try other methods of smoking cessation. To accomplish this, an early analysis of each subject up to week 6 was sent to the data management vendor to be analyzed by an outside consultant. All personnel dealing directly with the study remained blinded to both treatment and results of the analysis.

Four amendments to the statistical analysis plan were proposed on June 30, 2000. As they were not part of the original protocol, the sponsor did not feel it necessary to provide a formal protocol amendment.

Statistical amendment I proposed the pooling of data from centers too small to allow for assessment of the center by treatment interaction with the next smallest center, and for exploratory analysis, all UK centers were pooled together and all US centers were pooled together. It also provided a rationale for the pooling of continuous endpoints and responder endpoints if needed.

Statistical amendment II. Because European authorities recognize a 20 cpd cutoff as opposed to the US that uses a 25 cpd cutoff, this amendment proposed an additional summary of AEs in subjects who had smoked < 20 cigarettes/day and allocated to the 4mg group.

Statistical Amendment III. This amendment proposed using the chi-squared test to estimate differences in proportion between treatment groups when an AE occur $\geq$5% in any group. If the cells in a two-way table contained < 5 subjects Fisher's Exact test was to be used. The analysis was to be performed on the ITT population, subjects who took more than the median dose for the first two weeks, subjects who had smoked < 20 cpd, and subjects who had smoked < 25 cpd. This amendment was proposed to support the safety profile.

Statistical Amendment IV provides for the use of an appropriate non- parametric technique to validate the main results if the assumptions of the statistical analysis are violated. Note: Please see comments regarding secondary efficacy variables on page 26 of this review. [Item 8.D.3.8, pp. 46-50.]

Sponsor's Efficacy Results

While the study protocol allowed subjects to remain in the study for up to 12 months, the sponsor initially only provided detailed data and analysis of the ITT population for 6 months. However, the sponsor submitted an addendum to this report on April 23, 2001 after the final subject completed.

Primary Efficacy Variables

The sponsor defined the primary efficacy endpoint (success) as 28 days of continuous quit as measured at 6 weeks from the original quit date. Carbon monoxide (CO) measurements were used to measure abstinence. A ———————— was used and results recorded in the CRF. CO measurements were made at all visits (weeks 0, 1, 2, 4, 6, and 12 weeks, and 6 and 12 months post-quit) and was used to determine if a subject could remain in the trial. Determination of abstinence was begun on visit 4 (2weeks). Any subject who had a CO level of >10ppm on visit 4 (2 weeks) was considered a failure and was discontinued. Any subject who, after visit 4, reported smoking or showed a CO level >10ppm was also considered a treatment failure and discontinued.

The ITT analysis was made up on 1818 subjects. At 6 weeks the 2mg nicotine lozenge group showed a 46% quit rate while the matched placebo group showed 30 % quit rate. The 4mg nicotine lozenge group had a 49% quit rate compared to 21% for its matched placebo group. This resultant p value was a statistically significant difference with a $p < 0.00001$ for both 2 and 4mg groups.

Reviewer's Table 10

	2 mg Lozenge	**4 mg Lozenge**
	Success	**Success**
Nicotine	n=459 (46%)	n=450 (49%)
Placebo	n=458 (30%)	n=451 (21%)
p-value	<0.0001	<0.0001
95% C.I.	(1.59, 2.79)	(2.74, 4.96)

[Based on sponsor's table 5.4.1.1, p. 66 and Table 9.10.1.1.1, p.410]

A three months post-quit The results showed a 34% continuous quit rate for the 2 mg nicotine lozenge group compared to 22% for the matched placebo group with a statistically significant $p<0.0001$. The 4 mg nicotine lozenge group showed a 3 month continuous quit rate of 35% vs. 14% for their matched placebo group with a $p<0.0001$.

Reviewer's Table 11

	2 mg Lozenge	4 mg Lozenge
	Success	Success
Nicotine	n=459 (34%)	n=450 (35%)
Placebo	n=458 (22%)	n=451 (14%)
p-value	<0.0001	<0.0001
95% C.I.	(1.45, 2.66)	(2.45, 4.76)

[Based on sponsor's table 5.4.1.2, p. 68 and Table 9.10.2.1.1, p.414]

A six months post-quit The results showed a 24.2% continuous quit rate for the 2 mg nicotine lozenge group compared to 14.4% for the matched placebo group with a statistically significant $p=0.0002$. The 4 mg nicotine lozenge group showed a 6 month continuous quit rate of 23.6% vs. 10.2% for their matched placebo group with a $p<0.0001$.

Reviewer's Table 12

	2 mg Lozenge	4 mg Lozenge
	Success	Success

Nicotine	n=459 (24%)	n=450 (24%)
Placebo	n=458 (14%)	n=451 (10%)
p-value	0.0002	<0.0001
95% C.I.	(1.39, 2.78)	(1.89, 4.02)

[Based on sponsor's table 5.4.1.3, p. 69 and Table 9.10.3.1.1, p.418.]

This reviewer examined Tables 5.4.1.1, 5.4.1.2, and 5.4.1.3 and compared them with Tables 9.10.1.1.1, 9.10.2.1.1, and 9.10.3.1.1. No discrepancies were found.

An analysis of smoking cessation rate by gender was done at 6 weeks and the results reported in sponsor's Table 9.11.2. The results indicate similar success rates for both male and female subjects at both 2 and 4mg doses. The total male population was 788 and the total female population was 1030. Both males and females showed a better success rate over placebo in the 4mg group than in the 2mg group but this is consistent with overall results. Males showed better success rates over placebo in both 2mg and 4mg groups than females. See table below:

Reviewer's Table 13 **Summary of Smoking Cessation Rate at 6 Weeks by Sex**

Male	**2 mg Lozenge Success Rate**	**4 mg Lozenge Success Rate**
Nicotine	99/197 (50%)	104/195 (53%)
Placebo	55/184 (30%)	52/212 (25%)
Female		
Nicotine	112/262 (43%)	115/255 (45%)
Placebo	81/274 (30%)	42/239 (18%)

[Based on Item 8.D.5.4.1.2 and Sponsor's Table 9.11.2, pp. 67, 475.]

In order to assess whether increased nicotine lozenge usage was associated with improved efficacy, the sponsor analyzed the subjects taking more than the median number of nicotine lozenges vs. those taking less than the median number of nicotine lozenges and compared them to their comparable placebo groups. The median number of lozenges/day were 6.7 in the 2mg group and 8.2 in the 4mg group. The analysis showed that those taking higher numbers of nicotine lozenges had a higher quit rate at week 6 than those taking fewer lozenges. [Item 5.4.1.8.1, p.73.]

APPEARS THIS WAY
ON ORIGINAL

Reviewer's Table 14

Success Rate at 6 Weeks Stratified by Lozenge Use

	2 mg Lozenge Success Median Lozenge	**4 mg Lozenge Success Median Lozenge**

	Use=6.71/day	Use=8.17/day
High Lozenge Users (n=855) Used More Than Median Lozenge Use		
Nicotine Lozenge	120/n=208 (58%)	121/n=213 (57%)
Placebo Lozenge	66/n=221 (30%)	41/n=213 (19%)
95% C.I.	(2.13, 4.75)	(3.60, 8.61)
Low Lozenge Users (n=963) Used Less Than Median Lozenge Use		
Nicotine Lozenge	91/n=251 (36%)	98/n=237 (41%)
Placebo Lozenge	70/n=237 (30%)	53/n=238 (22%)
95% C.I.	(0.93, 1.99)	(1.65, 3.67)
P value*	0.0028	0.0067

* P value is based on a test for consistency of treatment effect in high and low lozenge users. [Based on sponsor's table 5.4.1.8.1.1, pp.74, 85.]

This reviewer compared values in the Table above with sponsor's Tables 9.12.1.1.1 and 9.12.1.2.1 [pp.477, 479] and found no inconsistencies.

Secondary Efficacy Variables

The sponsor also looked at effects of the nicotine lozenge on withdrawal and craving during the first two weeks post-quit. Their analysis found that the 4 gm group showed statistically significant reduction in withdrawal in week 1 with a $p<0.0001$ and in week 2 with a $p=0.0001$.

Craving for the 4mg group showed a statistically significant reduction in weeks 1 and 2 with a $p<0.0001$.

It should be noted that this reviewer looked at the data presented in Table 9.10.4.1.1 and found that P values for withdrawal symptoms were calculated 2 different ways in the 2mg group. One way used the difference in means and the other way used the difference in medians. The sponsor stated that because normality had been violated, they also used the Wilcoxon rank sum test for calculating difference in medians. Using the difference in medians, the 2 mg group only demonstrated a statistically significant reduction in withdrawal symptoms in week 1 with a $p=0.0166$ (week 2 showed no significant difference with a $p=0.1848$). The p value using the difference in means showed no statistically significant difference between 2mg nicotine and placebo at 1 ($p=0.0688$) week, but did show a statistically significant difference at 2 weeks (0.0309). After consultation with Dr. Stella Grosser, Biostat Reviewer, it was felt that since these were secondary endpoints, and that using either calculation method resulted in p values that were significant one week and not significant in the other, there was no cause for concern. After consultation with Dr. Celia Winchell, Addiction Drug Products Team Leader, it was felt that lower scores in the 2mg group may be attributed to the lower initial level of addiction and hence the

lower withdrawal symptoms. Note: Please see explanation of statistical amendment IV on p.23 of this review.

Craving scores were significantly reduced for the 2mg group in weeks 1 and 2 with p values of 0.0239 and 0.0269 respectively. The proposed labeling uses the phrase, "reduces the withdrawal symptoms including nicotine craving associated with quitting." The mixed result in the 2mg group is not unexpected, given the lack of standard approach to measuring withdrawal. The positive finding on the craving measure provides support for the labeling claim.
[Based on data from Item 8.5.5, Sponsor's Tables 5.4.1.4, 9.10.4.1.1, and Tables 5.4.1.5, 9.10.5.1.1, pp. 70-71, 86, 422-424, and 436-437.]

8 INTEGRATED REVIEW OF SAFETY

8.1 Findings vs. Labeling Claims

Safety was assessed by adverse events reports. Clinical laboratory measurements and vital signs were taken in the pharmacology studies but were taken during the course of this Study S1410043. [Items 6.4 and 6.5, p.121.]

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 label. Upper respiratory tract infection (URTI) was considered unrelated to study drug.

Reviewer's Table 15
Most Common Treatment Emergent AEs (≥5%)

BODY SYSTEM	% OF SUBJECTS (ITT POPULATION)			
	2mg NICOTINE	2mg PLACEBO	4mg NICOTINE	4mg PLACEBO

	LOZENGE n=459	LOZENGE n=458	LOZENGE n=450	LOZENGE n=451
Central and Peripheral nervous system disorders				
Headache	23 (5%)	27 (6%)	36 (8%)	15 (3%)
Gastrointestinal disorders				
Diarrhea	16 (4%)	10 (2%)	24 (5%)	17 (4%)
Flatulence	42 (9%)	33 (7%)	35 (8%)	23 (5%)
Heartburn	23 (5%)	10 (2%)	26 (6%)	4 (<1%)
Hiccup	15 (3%)	0	26 (6%)	0
Nausea	56 (12%)	22 (5%)	68 (15%)	24 (5%)
Respiratory system disorders				
Coughing	19 (4%)	13 (3%)	25 (6%)	12 (3%)
Sore throat	12 (3%)	12 (3%)	23 (5%)	18 (4%)
URTI	55 (12%)	45 (10%)	44 (10%)	29 (6%)

[Based on sponsor's Table 6.2.2.2.1 and 9.19.1.1, pp. 92-95.]

Nausea was the most frequently reported AE. Of the 56 subjects in the 2mg nicotine group who reported nausea, 29 were mild, 20 were moderate and 7 were severe. In the 4 mg nicotine group, with a total of 68 reporting nausea, 38 were mild, 23 moderate, and 7 were severe. In the 2 mg nicotine group 13 discontinued due to nausea and in the 4mg nicotine group 8 discontinued.

In the 2mg nicotine group flatulence was reported in 42 subjects, mild in 16, and moderate in 17, and severe in 9. In the 4mg nicotine group among 35 subjects who reported flatulence, 19 mild, 12 moderate, and 4 severe. In the 2mg nicotine group one discontinued due to flatulence and 2 discontinued from the 4mg group.

Of the 23 subjects who had heartburn in the 2mg nicotine group, 3 had severe symptoms. In the 4mg nicotine group 5 of the 26 who reported heartburn had severe symptoms. Two discontinued from the 2mg nicotine group and 2 discontinued from the 4mg nicotine group.

Diarrhea, hiccup, coughing, and sore throat were reported in greater than 5% in the 4mg group only. Of the 24 cases reported, 14 were mild and 2 were severe. Hiccup was mild in 19 of 26 cases and severe in

one. There were no discontinuations due to hiccup or diarrhea. Coughing was mild in 17 of the 25 subjects who reported it and severe in 3 cases. Sore throat was mild in 15 of 23 cases and severe in one case. There were no discontinuations due to coughing but one subject in the nicotine group discontinued due to sore throat.

Of the reported cases of headache in the 2mg nicotine group 5 of the 23 cases were severe and in the 4mg nicotine group 3 of the 36 cases were severe.

The sponsor made special note of subjects who were light smokers (< 20 or 76 subjects and <25 cpd or 226 subjects) who were assigned to the 4mg treatment group based on their time to first cigarette (< ½ hour). Usually assignment to heavy or light smoking groups is done on the basis of how many cigarettes a subject smokes in a day. Thus those some light smokers were assigned to the 4mg group. They create a valuable subgroup for analysis. The sponsor has compared the AE profile of this subgroup to another subgroup of smokers who smoked ≥ 20 or 25 cpd and were assigned to the 4mg lozenge group. Based on the table below, that there does not appear to be a clinical difference in AEs at the 4mg dose between those who smoked more than 20 or less than 20 cpd and between those who smoked more than 25 and those who smoked less than 25 cpd.

Reviewer's Table 16
Number of Smokers Reporting AEs Stratified by Cigarettes/day (cpd) for Subjects in 4mg Group

	Cigarettes/day			
	< 20	≥ 20	< 25	≥ 25
4 mg nicotine	55 (72%)	265 (71%)	162 (72%)	158 (71%)
placebo	29 (55%)	207 (52%)	114 (56%)	122 (50%)

[Based on Sponsor's Table 6.2.2.7.1, Item 8.D.3.6.2.2.7, p.103]

For the most part the safety profile was not significantly different. However, among the light smokers (<25 cpd) who received the 4mg dose, those who experienced headache, heartburn, hiccup, and nausea showed a statistically significant difference from placebo. And of these, only those who experienced headache, hiccup, and nausea also demonstrated a higher incidence than the heavy smokers did (≥ 25 cpd). [Item 8.D.3.6.2.2.7, pp.103, 104-106.]

This reviewer examined the raw data listings for the SAEs in the nicotine groups and for the deaths. No discrepancies were found.

8.2 Adequacy of Exposure and Safety Assessment

In Study S1410089, 24 subjects received all 9 doses. In Study S141009020 subjects got the 4mg nicotine lozenge 3 times. In Study S1410091, 26 subjects got 9 doses of the 2 and 4mg lozenge. In study S1410092, 65 subjects got a single dose of 3mg lozenge. In Study N96016, 14 subjects got 4mg lozenge two times. In Study N98001, 23 subjects got a single 2mg dose of the lozenge.

In Study S1410043, there were 1818 subjects that were randomized and exposed to either study drug or placebo for up to 24 weeks. They received either 2 or 4mg lozenges depending on the time until their first morning cigarette. They were to quit smoking and take the lozenges according to the following regimen:

Weeks 1-2 one lozenge every 1-2 hours
Weeks 7-9 one lozenge every 2-4 hours
Weeks 10-12 one lozenge every 4-8 hours
After 12 weeks 1-2 lozenges/day to stay abstinent

All lozenge use ended at 6 months. In the 2mg nicotine lozenge group the greatest mean use occurred at Week 2 (7.4) and the least use at Week 24 (0.2). In the 4mg nicotine group the greatest mean use occurred at Week 2 (9.1) and the least Weeks 23 and 24 (0.7). [Item 6.1, and sponsor's Tables 6.1.1, and 9.2.1.1, pp.87-88, 138-143.]

This reviewer compared the sponsor's Table 9.2.1.1, pp. 138-143 with Table 6.1.1 and found no discrepancies.

8.3 Review of the ISS

Deaths

There were no deaths reported in any of the clinical pharmacology studies or the abuse liability study. Three deaths were reported in Study S1410043 and they were all in the 4mg **placebo** group and were unrelated to study medication. The were no. 5931 at Center 82 which was a myocardial infarction, no. 5645 at Center 83 which was a brain aneurysm, and no. 5032 at Center 33 which was rupture of an aortic bypass graft. All thee deaths were sudden and unexpected. [Item 6.3. p.118, 120.]
This reviewer examined the raw data for AEs provided in dataset AE and compared the deaths to those reported in Item 6.3. There were no discrepancies.

Serious Adverse Events

There were no SAEs reported in any of the clinical pharmacology studies or the abuse liability study. In Study S1410043 there were 29 subjects who experienced a total of 33 serious adverse events. There were 9 (2%) in the 2mg nicotine group, 4 (1%) in the 2 mg placebo group, 12 (3%) in the 4mg nicotine group, and 4 (1%) in the 4mg placebo group. See next page for a copy of the sponsor's Table 6.3.1.2.1 that contains SAEs, deaths and discontinuations:

Reviewer's Table 17

Table 6.3.1.2.1: Summary of Serious Adverse Events: ITT Population

Centre/ Subject No.	Adverse Event	Severity	Relationship
2 mg Nicotine Lozenge Group			
30/0309	Melanoma (right thigh)	Severe	Unlikely
31/0350*	Pleurisy	Severe	Unlikely
33/0007*	Acute allergy	Moderate	Highly probable
82/1062	Non-insulin dependent diabetes mellitus(NIDDM)	Severe	Not related
83/0642	Hysterectomy	Severe	Not related
83/0643	Cervical cancer	Severe	Not related
87/0546	Chest pain	Severe	Unlikely
88/0757*	Angina pectoris Stenosis Hypercholesterolemia	Severe Severe Severe	Not related Not related Not related
91/1170	Congestive heart failure	Severe	Not related
2 mg Placebo Lozenge Group			
30/0474*	Cellulitis	Severe	Unlikely
31/0091	Fracture of lateral lower limbs Re-setting fractured lower limbs	Severe Severe	Not related Not related
33/0193*	Swollen left calf	Severe	Not related
86/1058	Pelvic inflammatory disease	Severe	Not related
4 mg Nicotine Lozenge Group			
31/5056	Depression	Moderate	Not related
31/5073	Bowel obstruction	Severe	Unlikely
31/5098	Head injury in road traffic accident	Moderate	Not related
31/5467	Worsening emphysema	Severe	Not related
32/5116	Skin cancer	Moderate	Not related
33/5415*	Fits	Mild	Not related
80/5903	Surgery to correct herniated disc	Moderate	Not related
83/5629	Chest pains	Severe	Unlikely
84/5723*	Cutaneous T-cell lymphoma	Severe	Not related
84/5727	Shortness of breath Angioplasty	Severe Severe	Not related Not related
84/5736	Pneumonia	Severe	Not related
87/5541	Bilateral inguinal herniorraphy	Moderate	Not related
4 mg Placebo Lozenge Group			
32/5277	Injury to foot requiring hospitalisation	Severe	Not related
32/5289	Lithotripsy	Moderate	Not related
33/5011*	Chest pain, myocardial infarction	Severe	Not related
33/5032*	Rupture of aortic bypass graft**	Severe	Not related
82/5931	Myocardial Infarction**	Severe	Not related
83/5645	Brain aneurysm**	Severe	Unlikely
90/5848	Surgery for herniated disc	Severe	Not related

Source: Data Listing 2.12.4
* Subject discontinued study treatment
** Subject died

[Copy of sponsor's Table 6.3.1.2.1, p.119.]
Besides the 33 SAEs listed in the table above, the sponsor notes only one drug related discontinuation and that was in No. 5843 at Center 90 who had chest pain, gas and heartburn. Of the 33 SAEs 32 were unrelated or unlikely to be related. One case of acute allergic reaction and windpipe constriction in the 2mg nicotine group was considered highly probably related. The intensity was recorded as moderate and the patient recovered after discontinuing the lozenge. Of the 32 SAEs, 11 discontinued because of the SAE. [Item 8.H.1.8]