OTC Drug Clinical Review

Division of Over-The-Counter Drug Products • HFD-560
Center for Drug Evaluation and Research • Food and Drug Administration
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NDA NO. 21-330

DRUG NAME Nicotine Polacrilex Lozenge
(2-mg and 4-mg)

SUBMISSION TYPE

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N-000	Feb 26, 2002		Resubmission (PK/Safety)	Review HFD-560

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PROPOSED INDICATION [redacted]

ADMINISTRATION Oral (buccal delivery)

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TABLE OF CONTENTS

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The recommendation for this NDA is ***Approval*** for OTC marketing, based on the following conclusions drawn from this NDA resubmission and from previous clinical studies. The further supportive evidence on comparability of safety profiles between the 4-mg lozenge and the 4-mg gum is expected from the committed phase VI clinical safety study.

1. The maximal plasma nicotine level achieved by the 4-mg nicotine lozenge seems to be comparable to the currently marketed OTC 4-mg nicotine gum at single and multiple dosing regimens, and comparable to the currently marketed OTC 21-mg nicotine patch at single dosing regimen.

2. The 4-mg nicotine lozenge at single and multiple dosing regimens appears to produce slightly higher total systemic nicotine exposure (AUC) than, but may be comparable to, the currently marketed OTC products, 4-mg nicotine gum and nicotine patches.

3. Post-marketing experience on the nicotine lozenge from the UK showed no serious adverse events associated with the nicotine lozenge (2-mg and 4-mg) during the 3-month spontaneous post-market report period.

4. Post-marketing experience on the nicotine patch and gum for prescription use showed no serious adverse events associated with both products during the 10-years spontaneous post-market report period (1984-1994).

5. Cigarette smoking produces the highest systemic nicotine exposure as compared with all nicotine replacement therapy products, including the 4-mg nicotine lozenge, at single and multiple dosing regimens.

6. The flat dose-response for certain effects on cardiovascular system, one of major targets of nicotine, may to some degree "buffer" effects of the slightly increased nicotine bioavailability from the 4-mg lozenge.

B. Recommendation on Phase 4 Studies and Risk Management Steps

The sponsor provided two phase VI study protocols in this resubmission in response to the Approvable Letter. The study designs have been reviewed by Dr. Linda Hu (HFD-560); and comments and recommendations have been forwarded to the sponsor. There are no additional recommendations on the phase VI studies.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Nicotine Polacrilex lozenge, 2-mg and 4-mg, is a nicotine replacement therapy (NRT) product through buccal delivery, indicated for smoking cessation aid (reduction of withdrawal symptoms, including nicotine craving, associated with quitting smoking). There were no new studies conducted and reported in this resubmission; only brief literature reviews with literature reprints were submitted to address the issues raised during the original NDA review cycle.

In the original NDA submission of December 14, 2000, the following clinical trial reports were submitted and the reviews were completed by HFD-170 and HFD-560 in 2001, as summarized in ***Table 1***.

Table 1. Clinical studies conducted and reviewed in the original NDA submission

Study Type	Study No.	Study Objective	Reviewer
PK (5 studies)	N98001	Single-dose, bioavailability	Dr. Shinja Kim, HFD-170
	N96016	Single-dose, Bioavailability	
	S1410090	Effects of misuse	
	S1410092	Bioequivalence	
	S1410091	Multiple-dose, Bioavailability	
Efficacy and Safety (2 studies)	S1410043	Randomized, double-blind, placebo control, multi-center	Dr. Harold Blatt, HFD-170
	S1410089	Abuse liability	Dr. Cynthia McCormick, HFD-170
OTC (4 studies)	S14100154	Home-use study	Dr. Linda Hu, HFD-560
	S140065	Expectation/acceptance	
	2117	Label comprehension	
	2204		

B. Efficacy

No efficacy data were provided in this NDA resubmission. The efficacy issue raised during the previous NDA review was inconsistency in dosing regimen between the proposed labeling and the efficacy clinical trial (q1-2 hours). The dosing regimen in the proposed labeling (———) may provides less effective (because less nicotine exposure) than the one tested in the efficacy trial (q1-2 hours). The sponsor was requested in the approvable letter to address this issue. The dosing regimen has been

amended to consistent with the efficacy trial in the updated labeling submission. Refer to the labeling review by IDS in HFD-560.

C. Safety

No new safety studies were conducted and reported in this NDA resubmission. In the original NDA submission, one pivotal clinical safety trial (included in the Study S1410043) was reported. Refer to the primary and secondary clinical reviews by HFD-170 for details. The outstanding safety issues raised from the first review cycle was that the 4-mg nicotine lozenge delivered more nicotine per dose than the currently-marketed 4-mg nicotine gum, and thus the safety of the 4-mg nicotine lozenge can not be fully supported by previous safety experience of the 4-mg nicotine gum.

In this resubmission, the sponsor provided literature information (brief reviews with literature reprints) to address these issues. The following summary is based on the sponsor's responses and the cited original literature reports.

1. ***PK comparison for nicotine gum chewing procedures:*** The metronome-chewing procedure (4-second interval) did not produce statistically significant differences in the PK profile compared to the ad-lib chewing method for both 2-mg and 4-mg nicotine gums. The metronome chewing tends to produce lower plasma nicotine levels than the ad-lib. This suggests that the differences in C_{max} (8% higher with the lozenge) and AUC (27% higher with lozenge) in PK study N96016 may be overestimates of what would occur compared to ad-lib chewing.

2. ***Single dose PK comparison with other nicotine products:*** The C_{max} for the 4-mg nicotine lozenge looks comparable to the 4-mg gum and nicotine patch; the $AUC_{0-\infty}$ is slightly higher than the gum (as indicated in the previous PK trial) but with high variations, which may be comparable as well. The AUC for the nicotine patch is not comparable to the lozenge at the single dose because the 24-hour continuing nicotine exposure per patch is not considered as a single dose but a multiple dose scenario. Both 4-mg lozenge and gum have a similar T_{max}, suggesting comparable absorption rate. The nicotine lozenge is at least 4 times faster to reach C_{max} than the patch but slower than inhalation nicotine exposure (such as inhaler and cigarette).

3. ***Multiple dose PK comparison with other nicotine products:*** The simulated $C_{max(ss)}$ for the 4-mg nicotine lozenge at q60-min x13 doses is slightly higher than, but seems to be comparable to, the 4-mg nicotine gum. The observed daily AUC (either AUC_{0-t} or $AUC_{0-\infty}$) at multiple dosing regimens for the lozenge and gum are not available in this and previous NDA submission to compare with each other and with the nicotine patch. Based on the single-dose and multiple-dose PK studies submitted in the original NDA, the 4-mg lozenge is likely to produce higher nicotine exposure than the 4-mg gum at multiple dosing regimen. In actual use (q1-hour up to 20 doses/day for the lozenge and up to 24 pieces/day for the

gum), the daily nicotine exposure may be comparable between the 4-mg lozenge and the 4-mg gum.

4. ***Flat dose-response to nicotine:*** Certain cardiovascular effects (heart rate and blood pressure) demonstrated a flat dose-response to nicotine. As one of major targets of nicotinic effects, the flat cardiovascular effects may to some degree "buffer" the toxic effects of slightly increased nicotine bioavailability from the 4-mg lozenge. However, there are the following limitations on this flat dose-response:

   (1) The flat dose-response is mostly limited to certain cardiovascular effects (heart rate and blood pressure, but not microcirculation);
   (2) Increasing time interval between two consecutive nicotine treatments decreased tolerance to the cardiovascular effects and the 3.5-hour interval completely restored nicotinic cardiovascular effects, suggesting transient tolerance and flat dose-response;
   (3) Previous clinical study (in the original NDA) demonstrated that the 4-mg nicotine lozenge had better smoking quit rates and also higher AE rate than the 2-mg nicotine lozenge, suggesting dose-dependence;
   (4) The post-market AE reports from UK showed that the more AE reports were received from the 4-mg nicotine lozenge users than from the 2-mg nicotine lozenge users, suggesting dose-dependence;
   (5) The post-marker spontaneous AE reports on nicotine patch and gum showed more AEs with the patch than with gum, suggesting that even continuing nicotine exposure may develop a limited tolerance to nicotine.

5. ***Cardiovascular effects of nicotine patches in smokers with coronary artery disease:*** Three clinical studies (two randomized control trials and one case-series study) from literature reports showed that nicotine patches (15-mg, 21-mg) did not induce significant cardiac toxicity in smokers with coronary artery disease and with or without concurrent cigarette smoking. This might be a valuable reference for risk assessment of the nicotine lozenge. However, the 4-mg nicotine lozenge has the higher C_{max} and faster nicotine delivery (shorter T_{max}) than nicotine patch at multiple dosing regimen, and the daily systemic nicotine exposure from the lozenge is not available for comparison. The acute cardiac effects of rapid higher nicotine loading from the 4-mg nicotine lozenge can not be assessed from these literature reports. The phase IV safety study with the nicotine lozenge and gum in smokers with cardiovascular diseases, as recommended by the Agency in the previous review cycle, should provide supportive evidence.

6. ***Post-market spontaneous AE reports on nicotine lozenge from UK:*** The 3-month post-market spontaneous AE reports on the nicotine lozenge (2-mg and 4-mg) marketed in UK showed no serious AEs associated with nicotine lozenge. The general spectrum of AEs associated with nicotine lozenges appears similar to that from the clinical trial submitted in the original NDA. The 4-mg nicotine

lozenge users experienced more adverse events than then 2-mg lozenge after adjusted with distribution of each dosage form.

7. ***Post-market spontaneous AE reports on nicotine patch and gum:*** The post-market AE reports on Rx nicotine gum and Rx nicotine patch retrieved from the FDA spontaneous AE report database (from 1984-1994) showed no serious adverse events associated with both products in the 10-years spontaneous. The more AEs in all categories were reported from the nicotine patch than from the nicotine gum. This may suggest the continuing nicotine exposure from the patch may develop a limited tolerance on certain pharmacological effects, and thus caused more AEs than the intermittent nicotine exposure from lozenge and gum.

D. Dosing

The approvable letter of October 19, 2001 indicated that the sponsor's proposed dosing regimen in the labeling, [redacted]-2-hour up [redacted] lozenges/day for the first 6 weeks, was not supported by the single efficacy study evaluated a dosing regimen, q1-2-hour up to 20 lozenges/day for the first 6 weeks. In the resubmission, the sponsor has amended the dosing regimen to q1-2-hour at the first 6 weeks and up to 20 lozenge/day. Refer to labeling review on the resubmitted labeling package (completed by IDS/HFD-560 in June 17, 2002).

E. Special Populations

1. Gender Differences

No new information was provided in the resubmission to evaluate safety and efficacy of nicotine lozenges based on gender. Clinical trial (S1410043) submitted in the original NDA found that female subjects experienced more AEs and showed lower smoking cessation rates than male subjects for both 2-mg and 4-mg nicotine lozenges. Refer to the primary clinical review and the secondary clinical review for the original NDA.

2. Age differences

No new information was provided in this resubmission to evaluate different effects of the nicotine lozenge in elderly and pediatric (teenager) populations. Previous clinical trial (S1410043) submitted in the original NDA showed that slightly higher AE incidence was found in the subjects over 55 years old than in those under 55.

3. Ethic/racial Differences

No clinical studies in previous and current submissions were conducted to address potential difference in nicotinic effects (efficacy and safety) among difference ethic populations. The sponsor noted in this resubmission from literature reports

that certain populations, such as Asians, metabolize nicotine more slowly than Caucasians, Hispanics, and African-Americans due to polymorphism of CYP2A6 (a major enzyme for nicotine metabolism). No studies have been conducted to evaluate safety and efficacy of the nicotine lozenge in different ethic populations. In the previous clinical trial submitted with the original NDA, 94% of subjects was the Caucasians.

4. Populations with certain medical conditions

   No clinical studies in the previous and current submission were conducted for safety evaluation of nicotine lozenges in subjects with cardiovascular disease, diabetics, renal disorder, or hepatic impairment. In this resubmission, the sponsor cited three clinical studies from literature and showed that nicotine patches (15-mg, 21-mg) did not induce significant cardiac toxicity in smokers with coronary artery disease and with and without concurrent cigarette smoking. The sponsor has committed to conduct a phase IV study to evaluate safety of the 4-mg nicotine lozenge in smokers with cardiovascular disorders and diabetics. The study protocol was submitted and is being reviewed by Dr. Linda Hu (HFD-560).

5. Pregnancy and lactation population

   No clinical studies were conducted in subjects with pregnancy or breast-feeding in the previous and current submission. A literature review regarding reproductive toxicity of nicotine was submitted in the original NDA and reviewed by a pharm/tox reviewer in HFD-170 in February 20, 2001. The standard pregnancy warning for the OTC drugs in this class will be used in the labeling of the nicotine lozenge.

6. Abuse liability in Teens and Adults

   The clinical abuse liability study of nicotine lozenge in teenage and adults submitted with the original NDA was reviewed by Dr. Cynthia McCormick. It was concluded that there was no significant signal regarding the abuse potential of this product by itself or compared with the currently marketed OTC product, Nicorette gum.

Clinical Review

I. Introduction and Background

This is a resubmission to address the pharmacokinetics (PK) and PK-related safety issues for the 4-mg nicotine polacrilex lozenge raised during the first review cycle for the original NDA submission.

Nicotine polacrilex lozenge (2-mg and 4-mg) is an alternative to currently-marketed nicotine polacrilex gum (2-mg and 4-mg) for using as a cigarette smoking cessation aid. The drug substance and nicotine delivery profile of nicotine lozenge are similar to the nicotine gum. The rationale for the lozenge form is more acceptable and easily used by smokers and thus probably better smoking cessation. In addition to the nicotine gum, there are many other nicotine replacement therapy products available in the US market (for either OTC or Rx marketing), as summarized in ***Table 2***, including nicotine inhaler, nicotine nasal spray, nicotine patch.

Table 2. Currently Marketed Nicotine Replacement Therapy Products in US

Proprietary Name	NDA or ANDA	Approval Date	Strength	Applicant	Market Status
Nicotine TD	A74-645	Oct-20-97	7-mg Patching 24-hr	SANO	Rx
	A74-611	Oct-20-97	14-mg Patching 24-hr	SANO	Rx
	A74-612	Oct-20-97	21-mg Patching 24-hr	SANO	Rx
Nicotrol	N20-714	May-02-97	4-mg Inhalation	Pharmacia & Upjohn	Rx
	N20-385	Mar-22-96	0.5-mg Nasal spray		Rx
	N20-536	June-03-96	15-mg Patching 16-hr		OTC
Nicoderm CQ	N20-165	Aug-02-96	7-mg, 14-mg, 21-mg Patching 24-hr	Aventis Pharm	OTC
Prostep	N19-983	Dec-23-98	11-mg, 22-mg Patching 24-hr	Elan Pharm	OTC
Habitrol	N20-076	Nov-12-99	7-mg, 14-mg, 21-mg Patching 24-hr	Novartis	OTC
Nicorette	N18-612	Feb-09-96	2-mg gum	GlaxoSmith Kline	OTC
		Dec-23-98	2-mg gum (mint)		OTC
		Sep-25-00	2-mg gum (orange)		OTC
	N20-066	Feb-09-96	4-mg gum		OTC
		Dec-23-98	4-mg gum (mint)		OTC
		Sep-25-00	4-mg gum (orange)		OTC
Nicotine Polacriflex	A74-507	Mar-15-99	2-mg gum	Watson Lab	OTC
	A74-707	Mar-19-99	4-mg gum		OTC

The original NDA for the nicotine polacrilex lozenge (2-mg and 4-mg) was submitted to the Agency on December 14, 2002. The clinical reviews were completed Dr. Harold Blatt (medical officer, Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170), and Dr. Linda Hu (medical officer, Division of OTC Drug Product, HFD-560). The conclusion from the first review cycle was ***approval*** for the 2-mg dosage form but ***approvable*** for the 4-mg dosage form due to the higher systemic nicotine exposure

than the marketed 4-mg nicotine gum. An ***Approvable Letter*** was issued to the sponsor on October 19, 2001, followed by an ***Advice Letter*** of February 15, 2000 from Dr. Charles Ganley (director, Division of OTC Drug product). The sponsor was advised to address the following outstanding issues for the 4-mg nicotine lozenge prior to final approval:

1. Provide data and information on nicotine concentrations comparing the metronome chewing method with ad-lib chewing for nicotine gum.

2. Provide information on the maximum concentrations achieved with single and repeat dosing with various nicotine products (e.g. lozenge, gum, transdermal).

3. Provide information to support the flat dose-response curve for the systemic effects.

4. Provide adverse event reports from countries already marketing the lozenge over-the-counter, behind the counter, or by prescription.

5. You will have to agree to two post-marketing studies (Phase 4 commitments) to further assess the safety of the product as follows:

   a. Conduct a study in subjects with relative contraindications for use (e.g. subjects who have underlying diseases such as diabetics mellitus or cardiovascular disease but are instructed by their physician to use a nicotine product). The N should be 200-300. A control group would be helpful for you in the analysis of any adverse events but is not required.

   b. Conduct a study where leaflets soliciting adverse event information are included in package sold in the OTC setting. The N should be 5,000-10,000 responses.

In this resubmission, the sponsor provided brief literature summaries and related literature reprints, and two phase VI study protocols in response to the above comments. The resubmission was dated on February 26, 2002, received by the Agency in April, 2002, and re-assigned to this reviewer on June 17, 2002. This review covers the sponsor's responses to the first 4 comments. The phase VI commitment submission is being reviewed by Dr. Linda Hu (HFD-560).

II. Clinically Relevant Findings From Chemistry, Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

II-1. The responses to the CMC issues raised in the approvable letter of October 19, 2001 was submitted to and reviewed by the CMC team co-located in HFD-170. Refer to chemistry review for details.

II-2. There were no outstanding issues for pharm/tox, microbiology and statistics from the first review cycle. No new information for these disciplines is contained in

this NDA resubmission. Refer to the primary reviews of each discipline for the original NDA submission.

III. Human Pharmacokinetics and Pharmacodynamics

III-1. Human Pharmacokinetics

The following review covers the sponsor's responses to two PK issues indicated in the approvable letter and the advice letter: differences in PK profile between metronome and ad-lib chewing methods for nicotine gums, and differences in PK profile of the 4-mg nicotine lozenge as compared with currently marketed nicotine products.

PK Comparison between Two Chewing Procedures for Nicotine Gums

The sponsor provided a brief literature review based on unpublished and published study reports to address the Agency's Comment #1: *Provide data and information on nicotine concentrations comparing the metronome chewing method with ad-lib chewing for nicotine gum.*

1. Single-dose PK comparison between metronome-chewing and ad lib-chewing methods for the nicotine gum (2-mg and 4-mg)

Summary data from an [redacted] were presented. Briefly,

[redacted]

[redacted]

[redacted]

2. Effects of gum chewing rates on nicotine release from nicotine gum and plasma nicotine level.

A study published by Nemeth-Coslett et al in 1988 (1) was cited to estimate effects of metronome-chewing rates for the 4-mg gum on plasma nicotine level and nicotine release from the chewed gums. Human subjects (*characteristics were not specified in the article*) were advised to chew 4 mg nicotine gum (*brand was not specified*) at intervals of 1, 2, 4 or 8 seconds for 20-minute. Plasma nicotine level was measured before and 40 minutes after chewing initiation. The residual nicotine in the chewed gum was measured (*time*

point was not specified). The other group of subjects received electromyography (EMG) monitoring on masticatory pressure induced by gum-chewing in order to determine compliance of scheduled chewing rates. The results suggest that

a. Chewing rates (different chewing intervals from 1 to 8 seconds) did not induce significant difference in plasma nicotine levels but the faster chew rate increased nicotine extraction from the chewed gum.

b. Increasing chew rates (or decreasing chewing interval) tended to increase plasma nicotine levels (no statistical significance due to small sample size for this study, n=6), which is different from what the sponsor stated.

c. Approximately one chew per 4-second interval could produce reliable compliance, which is also supported by other three publications (2-4) as the sponsor cited.

3. Rationales for metronome and ad-lib chewing methods for nicotine gum

The sponsor discussed rationales for both chewing methods based on literature reports. It was concluded that the chew and park ad-lib procedure appears to promote compliance and nicotine absorption, and the metronome procedure is preferable for standardization for comparison over intra- and inter-studies. However, based on the above PK comparison data, there were no significant differences in PK profile and variations of each parameter between two methods. Therefore, the actual use procedure, ad-lib chewing, should be used for clinical PK studies.

Conclusion and Comments (for PK profile in different chewing procedures)

1. [redacted]

2. [redacted]

PK Comparison between the 4-mg Nicotine Lozenge and Other Nicotine Products

The sponsor provided published literature reports to address Agency's Comment #2: *Provide information on the maximum concentrations achieved with single and repeat*

dosing with various nicotine products (e.g. lozenge, gum, transdermal). The PK profile from both single-dose and multiple-dose regimens was compared between the 4-mg nicotine lozenge and currently marketed nicotine products.

1. Single-Dose PK Comparison: The T_{max} and C_{max} of plasma nicotine level after single dosing were extracted from literature for nicotine inhaler (Rx), nasal spray (Rx), patch (OTC), and cigarette, as compared with the nicotine gum (OTC) and the 4-mg nicotine lozenge from the original NDA submission (***Table 4***). The AUC data were extracted from the original publications by this reviewer.

   The C_{max} of the 4-mg nicotine lozenge was approximately half of Rx nicotine inhaler and OTC nicotine patch (21-mg). The nicotine lozenge was also slower to reach peak plasma nicotine level than the nicotine inhaler and cigarette, but at least 4 times faster than the nicotine patch. The $AUC_{0-\infty}$ for the 4-mg nicotine lozenge was lower than that for nicotine patch and nicotine nasal spray. It should be noted that the PK parameters for the nicotine patch were obtained from 24-hour exposure. For the reasonable PK comparison with the nicotine patch, accumulated daily PK parameters from the 4-mg lozenge should be provided for appropriate comparison (see the following Multiple-dose PK for further discussion).

   The sponsor stated that "A transdermal patch can provide comparable or higher level of plasma nicotine with one hour of application than would be by the 4-mg nicotine lozenge". It looks that the C_{max} from the 4-mg lozenge at the single dosing regimen is less than the plasma nicotine level produced by the 21-mg Nicoderm (Alza) at approximately 1-1.5 hours after patch application, as seen in ***Figure 2*** (adapted from the original publication (5)). However, the comparison was made between the multiple dosing regimen for the patch (24 hours continuing exposure) and the single dosing regimen for the lozenge. The C_{max} for the lozenge after daily multiple doses will be likely higher than patch. The same differences might be seen for the AUC comparison between the patch and the lozenge.

   As indicated in the primary biopharm review (July 2001) for the original NDA submission, the 4-mg nicotine lozenge achieved 8% higher C_{max} and 27% higher AUC0-∞ than the 4-mg gum in the single dosing regimen (the PK study N96016). The differences for both studies were slightly beyond the bioequivalence limit (90% confidence interval for the ratio of test and reference products). There were high intra-study and inter-study variations in PK measures for the 4-mg nicotine lozenge and gum (***Table 5***). The Cmax and AUC0-∞ for the 4-mg lozenge seem to be close to the 4-mg gum, which may be comparable. However, the impact of the difference on safety, and the comparability in safety profile between the lozenge and gum need to be determined by phase IV safety study as proposed by the sponsor.

Table 4. Plasma Nicotine PK Profile following **Single-Dose** of the 4-mg Lozenge and Other Nicotine Products

Nicotine Products	T_{max} (min)	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng·hr/ml)	Reference
Nicotine lozenge 4-mg	58 ± 18	7.8 ± 2.4	30.8 ± 9.9	Study *S1410090* in NDA
Nicotine lozenge 4-mg	66 ± 18	10.8 ± 4.7	44.0 ± 26.5	Study *N96016* in NDA
Nicorette gum 4-mg	54 ± 12	10.0 ± 2.9	34.6 ± 17.6	
Nicorette gum 4-mg	60 ± 15	11.0 ± 3.9	40.9 ± 30.4	Circa/Watson Pharm†
Nicotine inhaler 10-mg	6.7 ± 0.3	25.4 ± 5.4	189 ± 40 (arterial, 0-45 min)	Lunell, 2000 (6)
Cigarette 0.9-mg	6.4 ± 0.4	22.4 ± 3.9	543 ± 93 (arterial, 0-45 min)	
Nasal Spray 1-2.5 mg	17.6 ± 13	8.2 ± 4.0	186.8 ± 93.5 (0-30 min)	Guthrie, 1999 (7)
Nicoderm 21-mg (Alza)	576 ± 444	22.7 ± 4.3	412 ± 87‡	Gupta, 1995 (8)
Nicoderm 21-mg (Alza)	228 ± 162	21.9 ± 8.9	328 ± 144‡	Fant, 2000 (5)
Nicoderm 21-mg (Novartis)	600 ± 222	17.6 ± 6.4	290 ± 108‡	
Nicoderm 15-mg (Pharm-Up)	390 ± 162	11.9 ± 3.8	165 ± 54‡	

The table was prepared based on the sponsor's table (in page 21) and the cited original publications.

† Bioequivalence study for two 4-mg nicotine gums conducted by Circa/Watson Pharmaceuticals for ANDA74-707 in 1996. The PK parameters were extracted from raw data provided in "References" of this resubmission.

‡ The PK parameters were determined from plasma (venous) nicotine measurement during the first 24 hours after initial patching, AUC0-24hr, which was 24-hour continuing exposure (considered as multiple dosing regimen).

Table 5. Variations of PK measurements in a previous single-dose PK study on the 4-mg nicotine lozenge and gum

PK Parameter	Study N96016†		Study S1410090†	Circa/Watson‡
	4-mg Lozenge (n=12)	4-mg Gum (n=12)	4-mg Lozenge (n=22)	4-mg Gum (n=24)
C_{max} (ng/ml)	10.8 ± 4.7 (43%)*	10.0 ± 2.9 (29%)	7.8 ± 2.4 (31%)	11.0 ± 3.9 (35%)
T_{max} (hours)	1.1 ± 0.3 (27%)	0.9 ± 0.2 (22%)	0.97 ± 0.3 (31%)	1.0 ± 0.25 (25%)
$AUC_{0-\infty}$ (ng.hr/ml)	44.0 ± 26.5 (60%)	34.6 ± 17.6 (51%)	30.8 ± 9.9 (32%)	40.9 ± 30.4 (74%)
$T_{1/2}$ (hours)	2.3 ± 0.6 (26%)	2.1 ± 0.7 (33%)	2.6 ± 1.3 (50%)	2.2 ± 0.8 (36%)

† Data are extracted from the primary biopharm review completed in July 2001

‡ Bioequivalence study for two 4-mg nicotine gums conducted by Circa/Watson Pharmaceuticals for ANDA74-707 in 1996. The PK parameters in the table were extracted from raw data contained in "References" of this resubmission (page 381).

* The numbers in the parentheses are the ***coefficient of variation***.

2. Multiple-dose PK Comparison The sponsor provided steady state C_{max} ($C_{max(ss)}$) of plasma nicotine for currently marketed nicotine products (inhaler, nasal spray, patch and cigarette) from literature and compared with those of the 4-mg nicotine lozenge and gum from the previous PK study submitted in original NDA, as summarized in ***Table 6***.

   The $C_{max(ss)}$ for the 4-mg nicotine lozenge simulated to q60-min x13 doses was 34.9 mg/ml as per the primary biopharm review (completed by Dr. Shinja Kim in July 2001). This is slightly higher than the sponsor's simulated result, 32.4 mg/ml, reported in previous and current submission. As indicated in the primary biopharm review, the sponsor used an inappropriate prediction error for the simulation and thus resulted in a lower simulated $C_{max(ss)}$.

   In ***Table 6***, the 4-mg nicotine lozenge dosed at q1-hour for 13 doses will achieve the highest steady state C_{max} in all nicotine replacement therapy products (Rx and OTC uses). The simulated $C_{max(ss)}$ for the 4-mg lozenge is 8% higher than the 4-mg nicotine gum ($C_{max(ss)}$=32.3 ng/ml), the second highest NRT product.

   The daily (accumulated) AUC data at the multiple dosing regimen are not available for comparison between the lozenge and those NRT products. Base on the information from literature, the systemic nicotine exposure from the 4-mg lozenge and gum might be comparable to the patch that provides the 24-hour continuing exposure and bypasses the first-pass hepatic metabolism. The difference in exposure nature may further influence their safety profiles. As suggested in a post-market spontaneous AE report study (see Safety section for details), the patch users experienced more AEs than the gum users.

The cigarette smoking produced highest systemic nicotine exposure in all nicotine products, including the 4-mg nicotine lozenge, at both single-dose and multiple-dose regimens based on literature reports. There are many toxic components contained in cigarette smoking in addition to nicotine; nicotine alone or combined with other components may play an important role in cigarette smoking-induced toxicity. The nicotine replacement therapy will prevent consumers from exposure to other toxic components of cigarette and thus the benefit may relatively outweigh overall risks. However, the safety margin of nicotine can not be based on the known harmful cigarette product.

Table 6. Plasma Nicotine PK Profile at the Steady State Following **Multiple-Dose** of the 4-mg Nicotine Lozenge and Other Nicotine Products

Nicotine Products	Dosing Interval	Cmax (ss) (ng/ml)	Reference
Nicotine lozenge, 4-mg	1 piece/90-min x 9	26.0 ± 13.1†	*S1410091* in NDA
Nicotine lozenge, 4-mg	1 piece/60-min x 13	34.9†	Simulated from the single-dose study *N96016* in NDA
Nicotine gum, 4-mg	1 piece/60-min x 13	32.3 ± 13.7	*S1410091* in NDA
Sublingual tablet, 2-mg	2 mg/hr x 12	13.2 ± 3.1	Molander, 2001 (9)
Nicoderm, 21-mg patch	1 piece/24-hr x 3	27.8 ± 10.9‡	Fant, 2000 (5)
Nicotine inhaler, 4-mg	80 deep inhalations over 20 min/hr x10 hr	22.5 ± 7.7	PDR 2002
Nasal spray, 1-mg/dose	3 doses/hr x 11	18.2 ± 9.8	Schneider, 1996 (10)
Cigarette, 1-mg	1 Cig/30-min x 30/day	50.8 ± 21.9	Gupta, 1995 (8)

The table was prepared based on the sponsor's Table I in page 20 of the resubmission and based on the cited original literature reports. $C_{max(ss)}$ is the maximal plasma nicotine level at steady state.

† adapted from the primary biopharm review (July 2001)

‡ Three patch brands (one 15-mg, two 21-mg) were tested in the study, and only one with the highest C_{max} was cited in the table. See ***Table 7*** for detailed comparison among the three patches.

3. Multiple-dose PK Comparison with Nicotine Patches: The PK parameters of three currently marketed nicotine patches -- 15-mg Nicoderm (Pharmacia-Upjohn), 21-mg Nicoderm (Novartis), 21-mg Nicoderm (Alza) -- were extracted from a clinical study published by Fant et al in 2000 (5). The study included 25 subjects using double-blind, randomized, crossover design (with 4-day wash-out interval). The subjects used each patch for 3 consecutive days. The steady-state PK parameters at days 2-3 (48-72 hours) were simulated from the observed plasma nicotine data of the first 24

hours (***Figure 2***) and the elimination half-life of 3 hours. The results are summarized in ***Table 7.***

For comparison, multiple-dose PK data for the 4-mg nicotine lozenge and gum extracted from the primary biopharm review are incorporated into the table. The simulated C_{max} for the 4-mg nicotine lozenge is 25-184% higher than three nicotine patches (different strengths and brands). Both nicotine lozenge and nicotine gum reach the maximal plasma nicotine level much faster (shorter T_{max}) than nicotine patches, suggesting a different absorption rate between skin and buccal mucosa.

The AUCss is not comparable between the lozenge/gum and the patch based on the literature information. The "AUCss" for patch is actually accumulated daily AUC (during 24-hour continuing nicotine exposure), but the "AUCss" for the lozenge or gum was the AUC within a dosing interval at plateau (or steady state), not accumulated daily AUC. The sponsor claimed in page 24 of the resubmission that "Daily AUCs that are comparable or exceed those produced by projected typical lozenge use (based on the pivotal clinical efficacy study and on modeled PK data)". There are no experimental data provided in this and previous NDA submission, nor in literature, to support this statement.

Table 7. PK Profile of Nicotine Patch at the Steady-State with Comparison to the 4-mg Nicotine Lozenge and Gum Following Multiple Dose Administration

PK Parameter	Nicotine Patch†			4-mg Nicotine Lozenge (q60-min x13)	4-mg Nicotine Gum (q60-min x13)
	Brand-1 15-mg/16 hr	Brand-2 21-mg/24 hr	Brand-3 21-mg/24 hr		
AUC_{ss} (ng.hr/ml)	161 ± 52.7	295 ± 111	332 ± 146	Unknown	Unknown
C_{max} (ng/ml)	12.3 ± 3.8	19.5 ± 7.4	27.8 ± 10.9	34.9‡	32.2 ± 13.7
C_{min} (ng/ml)	1.53 ± 0.96	13.0 ± 5.7	11.9 ± 5.7		26.9 ± 12.8
T_{max} (hr)	6.0 ± 2.8	8.0 ± 2.2	2.8 ± 1.5		0.5 ± 0.2

The table was prepared based on the sponsor's Table 3 in page 25 of the resubmission and on the Fant's original publication (5).

† Nicotine patch Brand-1: Pharmacia & Upjohn; brand-2: Novartis; Brand-3: Alza. The AUCss (48-72 hours) for all three patches was simulated from the first 24-hour observed data (after initiation of first patching, which is daily accumulated AUC.

‡ Simulated data provided by biopharm reviewer; the daily AUC for the lozenge and gum at multiple dosing regimens are not available from this and previous NDA submission.

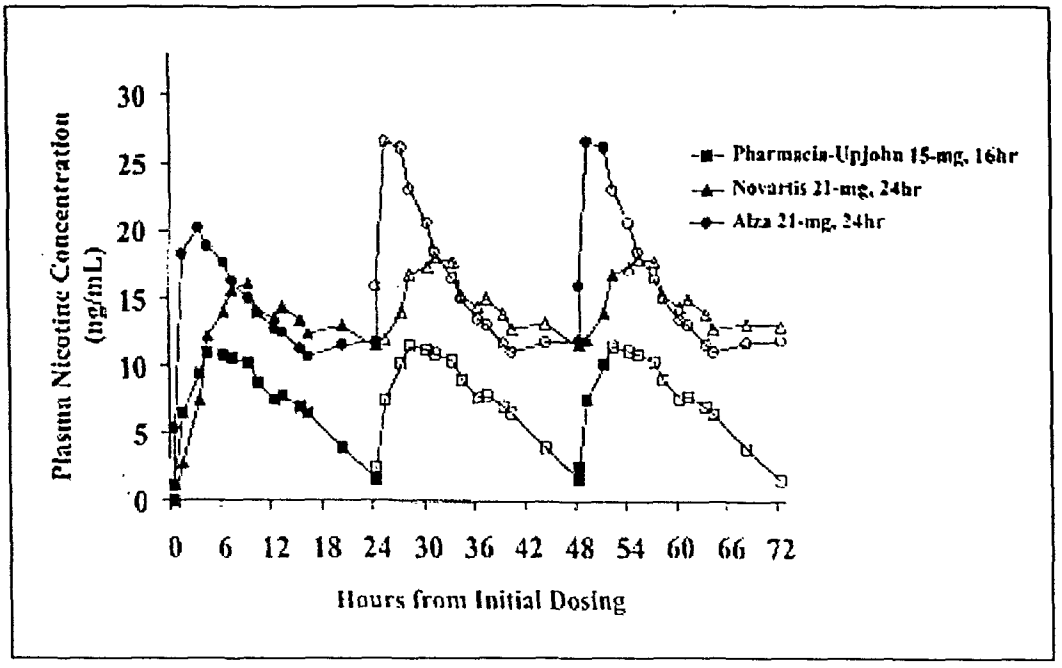

Figure 2. Plasma nicotine kinetics in human subjects (n=25) after receiving three different nicotine patches (15-mg, Pharmacia-Upjohn; 21-mg, Novartis; 21-mg, Alza). The first 24-hour data were observed, which were used for simulation of the plasma nicotine profile from 24-72 hours. The figure is adapted from the Fant's original publication (5).

4. Polymorphism on nicotine metabolism

It is known that certain human population, such as Asian, metabolize nicotine more slowly than others such as Caucasians, Hispanics or African-American. This is due to genetic polymorphism on CYP2A6, a major enzyme for nicotine metabolism (11). The sponsor cited several literature reports in the submission to support this. The 4-mg nicotine lozenge will very likely produce even higher plasma nicotine level in certain populations with slow metabolic rate. The sponsor stated that because of the "flat" dose-response, the higher plasma nicotine will unlikely cause "systemic toxicity". As discussed in below, the flat dose-response to nicotine is only limited to certain cardiovascular effects but not to systemic toxicity. The sponsor further stated that many Asians have used nicotine patch (1% of users according to GlaxoSmithKline data) and no serious toxicity has been reported. However, no literature and data for this regard were provided in this submission. Although the polymorphism on nicotine metabolism is a class issue for all nicotine replacement therapy products, the 4-mg nicotine lozenge produces relatively higher nicotine availability than other NRT products and special attention should be paid to certain consumer populations during post-market safety monitoring on this product.

5. Drug-drug interaction

Nicotine may interact with other drugs on the levels of metabolism and pharmacological actions. The target patient/consumer populations are often under certain medications while using this product. Some medications may alter metabolism of nicotine (thus PK profile) and influence functional activity of adrenergic receptors (through catecholamines), for example, β-adrenergic receptor antagonist propranolol for anti-hypertension therapy. No studies in this and previous NDA submissions address this issue. However, like the polymorphism on nicotine metabolism, this could be addressed as a class issue and by post-market safety monitoring.

Conclusion and Comments (for PK Comparison)

1. With single dosing regimen, among currently-marketed nicotine products (gum, patches, inhaler, nasal spray, cigarette), the C_{max} and $AUC_{0-\infty}$ for the 4-mg nicotine lozenge was lower than those for the Rx nicotine inhaler and cigarette. The C_{max} for the 4-mg nicotine lozenge looks comparable to the 4-mg gum and nicotine patch; the $AUC_{0-\infty}$ is slightly higher than the gum (as indicated in the previous PK trial) but with high variations (***Table 5***). The AUC for the nicotine patch is not comparable to the lozenge due to different dosing regimens, the 24-hour continuing nicotine exposure (considered as a multiple dose scenario). The nicotine lozenge is at least 4 times faster to reach C_{max} than the patch but slower than inhalation nicotine exposure (such as inhaler and cigarette).

2. With multiple dosing regimen, among currently-marketed nicotine products (gum, patches, inhaler, nasal spray, and cigarette), the simulated $C_{max(ss)}$ for the 4-mg nicotine lozenge at q60-min x13 doses is slightly higher than, but seems to be comparable to, the 4-mg nicotine gum. The observed daily AUC (either AUC_{0-t} or $AUC_{0-\infty}$) at multiple dosing regimens for the lozenge and gum are not available in this and previous NDA submission to compare with each other and with the patch. Based on the single-dose and multiple-dose PK studies submitted in the original NDA, the 4-mg lozenge is likely to produce higher nicotine exposure than the 4-mg gum at multiple dosing regimen. In actual use (q1-hour up to 20 doses for the lozenge and up to 24 pieces for the gum), the daily nicotine exposure may be comparable between the 4-mg lozenge and the 4-mg gum. The phase VI comparative safety study (between the lozenge and gum), as recommended by the Agency from the previous review cycle, should provide supportive evidence on the comparability.

3. Cigarette smoking achieves the highest systemic nicotine exposure in all nicotine replacement therapy products, including the 4-mg nicotine lozenge, in a single and multiple dosing regimens.

4. All PK data for comparison were based on literature reports with differences in study designs, subjects, procedures, data process, etc. In fact, the inter-study and intra-study variations have been shown in the previous PK studies, as seen in the ***Table 5***. The comparability in safety profile between the lozenge and the gum will be justified by the phase VI safety study, as recommended by the Agency.

5. Polymorphism on nicotine metabolism and potential drug-drug interaction are known for all nicotine replacement therapy products. These could be addressed as class issues and by post-market safety monitoring.

III-2. Human Pharmacodynamics:

The literature information provided in the resubmission related to human pharmacodynamics was the flat cardiovascular response and tolerance to nicotine. The most published literature reports cited by the sponsor were [redacted]

Flat Cardiovascular Response to Nicotine

The following studies from the literature suggest that the flat dose-response to nicotine is only limited to certain cardiovascular effects (such as heart rate and blood pressure), and may not be applicable to nicotine-induced systemic effects.

a. Intravenous infusion of nicotine increased HR and BP to peak at 10 minutes but not further increased for continued IV infusion of nicotine up to 30 minutes (suggesting response plateau); less response to the same nicotine dose at next dosing (suggesting development of tolerance) (12).

b. Smoking cigarettes containing high nicotine increased high plasma nicotine level as compared to those with low nicotine and usual brand cigarettes, but did not induce significant change in heart rates (13).

c. Increasing doses of nicotine delivered by patches (21, 42, or 63 mg nicotine per 24 hour) increased plasma nicotine level but did not induce significant change in heart rate and blood pressure, with or without concomitant cigarette smoking (14).

d. Rapid nicotine tolerance development was noted in 4 publications; 3 of them from [redacted] and co-workers (15-17). The cardiovascular tolerance (heart rate and blood pressure) (16, 17) and plasma epinephrine and metabolic rate (17) were developed rapidly. However, the cardiovascular effects of nicotine were completely restored after 3.5-hour interval (16). One case study report demonstrated a female patient developed tolerance to general nicotine toxic effects after skin exposure to high dose of nicotine sulfate (Black Leaf 40) (15).

e. An in vitro electrophysiology study of rat neuronal nicotinic receptors demonstrated that nicotine induced desensitization of nicotinic receptors in Oocytes expressing the rat neuronal nicotine receptor mRNA (18).

Nicotinic Effects of Rapid and Slow Delivery of Nicotine

The sponsor stated that slow nicotine delivery/loading (to circulation) from nicotine lozenge would produce less nicotinic toxicity than rapid nicotine delivery such as cigarette. The argument was mainly based on the study published by Porchet et al in 1987 (19). The study was conducted in rabbits and 7 healthy smokers treated with IV infusion of nicotine followed by monitoring blood nicotine level, heart rate and blood pressure. The results showed that rapid loading/delivery of nicotine resulted in higher cardiovascular effects than slow loading/delivery system. Additionally, the sponsor stated that nicotine delivered to the brain within 10-15 second of a cigarette puff, but 4-mg nicotine lozenge and gum deliver nicotine to the brain reaching peak level in 45-60 minutes, but the sources and details of these information were not indicated.

Inhalation administration of nicotine products (such as cigarette and nicotine inhaler) may achieve peak plasma nicotine level more rapid than other administration routes (such as transdermal and buccal or GI deliveries), as shown in the above ***Table 4*** (single-dose PK comparison). It is possible that the slow nicotine delivery through nicotine lozenge may produce less acute cardiovascular and central nerve system effects than the rapid delivery such as cigarette and inhalation. But the lozenge and gum will expect more nicotinic effects than the patch because the lozenge and gum have a shorter T_{max} (or faster loading) than the patch (***Table 4***). A post-market spontaneous AE study (see below) showed that the patch users experienced actually more AEs than the gum. This suggests that effects of the loading rate of nicotine are more complicated than expected.

Conclusion and Comments (for the flat dose-response)

Certain cardiovascular effects (heart rate and blood pressure) demonstrated a flat dose-response to nicotine. As one of major targets of nicotinic effects, the flat cardiovascular effects may to certain degree "buffer" the toxic effects of slightly increased nicotine bioavailability from the 4-mg lozenge. However, there are the following limitations on this flat dose-response.

1. The dose-response of nicotine appears to "plateau" for certain cardiovascular effects such as heart rate and blood pressure, which can not be extrapolated to nicotine-induced systemic effects/toxicity. In a reference article (12) that the sponsor cited, the clear nicotine dose-dependent decrease in skin temperature was noted, and no plateau was reached in the study, suggesting that effects of nicotine on microcirculation under the same experimental conditions was not "flat".

2. Increasing time between two consecutive nicotine treatments decreased tolerance to the cardiovascular effects and the 3.5-hour interval completely restored nicotinic cardiovascular effects, as indicated in the other reference article (16) that the sponsor cited. This suggests that the flat dose-response and tolerance to nicotine is transient, and it may be more applicable to continuing nicotine exposure than intermittent exposure.

3. Previous efficacy and safety study in the original NDA submission showed that the 4-mg nicotine lozenge had better smoking quick rates and higher AEs than the 2-mg nicotine lozenge, suggesting dose-dependent nicotinic effects.

4. Post-marketing AE reports on nicotine lozenge marketed in UK (see below ***Sponsor's response to the Agency's Comment #4*** for details), the 4-mg nicotine lozenge users experience more AEs than the 2-mg nicotine lozenge, suggesting systemic nicotinic effects were dose-dependent.

5. Postmarketing AE reports on nicotine gum and nicotine patch retrieved from the FDA spontaneous AE report database (from 1984-1994) showed that the nicotine patch had much more AEs than the nicotine gum. Although there are many limitations on the spontaneous AE reports, the results suggest that the continuing nicotine exposure from the patch may only develop a tolerance on certain nicotinic effects.

IV. Description of Clinical Data and Sources

1. [redacted]

2. Brief summaries/reviews based on published literature, including reprints, to address other PK and PK-related safety issues (flat dose-response);

3. Spontaneous post-marketing AE reports from UK during 3-month marketing period (from Oct 1, 2001 to Jan 27, 2002), including a brief summary and spread data sheet of individual case reports.

V. Clinical Review Methods

The whole resubmission by the sponsor, including brief literature summaries and cited major reprints, was reviewed in this division (HFD-560).

VI. Integrated Review of Efficacy

No efficacy data were provided in this NDA resubmission. The efficacy issue raised during the previous NDA review was the inconsistency in the dosing regimen between the proposed labeling and the efficacy clinical trial. Refer to the primary clinical review (completed by Dr. Harold Blatt in May 23, 2001), the secondary clinical review (completed by Dr. Celia Winchell), and the OTC review (completed by Dr. Linda Hu in July 17, 2001) for details. The sponsor was requested in the approvable letter to address this issue. The updated labeling has been submitted and the dosing regimen has been amended to q1-2 hr up to 20 lozenges per day, which is consistent with the dosing regimen studied in their efficacy trial. Refer to the labeling review for the labeling resubmission completed by IDS (Mary Robinson) in HFD-560.

VII. Integrated Review of Safety

No new safety studies were conducted and provided in this resubmission. The following safety review was based on the literature articles and spontaneous post-market AE reports from UK.

Safety Evaluation on Nicotine Patch in Smokers with Cardiovascular Disease

The sponsor cited three clinical studies conducted in smokers with cardiovascular diseases and using nicotine patch (20, 21), published by Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease in 1994 (21), Joseph et al in 1996 (22), and Mahmarian et al in 1997 (20). Two of studies were randomized placebo-control clinical trials and one prospective case-series study.

The main results from the three studies are summarized from the original publications in ***Table 8***. The studies suggest that nicotine exposure through transdermal routes did not induce significant cardiac toxicity in smokers with confirmed coronary artery diseases. However, the Cmax obtained with Nicoderm patch was still lower than the 4-mg nicotine lozenge in a multiple dosing regimen; the Tmax for the 4-mg nicotine lozenge was much shorter than nicotine patches, as indicated in ***Table 4***. The risk assessment from the nicotine patch studies may not be fully applicable to the nicotine lozenges, although they are valuable references.

Table 8. Cardiovascular effects of Nicoderm in smokers with coronary artery diseases

Study Type	Subject	Treatment & Observation	Main Results		Publication
			Plasma Nicotine	Clinical Findings	
Randomized double-blind Placebo-control multi-center	156 smokers with CAD; 74 Nicoderm, 79 Placebo	14-mg or 21-mg for 24 hrs x1-4 wks; Monitored up to 5 wks	14.1 ng/ml for Nicoderm/quit smoking; 21.1 ng/ml for Nicoderm/not quit smoking; 10.7 ng/ml placebo/not quit smoking	Nicoderm did not affect angina frequency, overall cardiac symptom, nocturnal events, arrhythmia, or episodes of ischemic ST depression; Smoking cessation: 36% for Nicoderm and 22% for placebo ($p<0.05$).	*Arch Intern Med* 1994 (21)
Randomized double-blind placebo-control multi-center (10 VAMC)	584 (576 male) with CAD; 294 Nicoderm, 290 Placebo	21-mg x 6 wks, 14-mg x 2 wks, 7-mg x 2 wks (total 10wks); Monitored up to 14 wks (at 1st, 6th, 14th)	Not monitored	Nicoderm did not significant increase cardiovascular events in smokers with CAD; Smoking cessation in the subjects was limited. Patch compliance at wk 6: 73% Nicoderm, 56% placebo	*N Engl J Med* 1996 (22)
Prospective single center	40 smokers with CAD All Nicoderm	14-mg for 24 hrs x 3 days followed by 21-mg for 24 hrs x 3 days	15.8 ng/ml for baseline (before patching); 24.2 ng/ml for 14-mg and 30.4 ng/ml for 21-mg at day 3.	Nicoderm significantly reduced exercise-induced myocardial ischemia (T-201 SPECT): 17.5% - 12.6% - 11.8 % (at baseline, 14-mg/day-3, 21-mg/day-3). 74% quit smoking during trial – contributed improvement of myocardial perfusion.	*J Am Coll Cardiol* 1997 (20)

The table was summarized from the original publications, as cited, and the conclusions were drawn by this reviewer.
CAD: Coronary artery disease with confirmatory diagnosis.

Post-Market AE Reports on Nicotine Gum and Patch

The sponsor provided a literature report (23) in which a group of the FDA researchers retrieved and analyzed the post-marketing AE reports on Rx nicotine gum and RX nicotine patch in the FDA *MedWatch* adverse drug event database. About 90% of the AE reports were originally submitted by manufacturers. During the 10-year Rx marketing period (from 1984 to 1994), there were [redacted] new prescriptions for gum and [redacted] for patch (strengths for both products were not specified) and the 5,129 AE reports were received. In general, much more AE reports were associated with nicotine patch than with nicotine gum. The detailed distribution of AEs between the two nicotine products is summarized in ***Table 9***.

The AE association with age, gender, medical history, concurrent smoking, outcomes and geographic distribution (from US and/or other countries) for those cases, as well as association with strengths of both nicotine products was not reported and discussed. Although there are many limitations of using spontaneous AE reports, this AE analysis suggests that continuing nicotine exposure, such as from the patch, may cause more AEs than non-continuing exposure, such as from gum and lozenge.

Table 9. Post-marketing AE reports on Rx nicotine gum and Rx nicotine patch received by the FDA from 1984-1994

	Nicotine Gum	Nicotine Patch
Marketing History	2-mg since 1984 and 4-mg since 1991 for Rx; since 1996 for OTC	5-21 mg since 1991-1992 for Rx; 7-21 mg since 1996 for OTC
Total New Rx	[redacted]	[redacted]
Total Case Number per Year (Reported to FDA MedWatch)	56	227
Total AE number: 5,129 (Reported to FDA MedWatch)	not presented	not present
AE category		
GI-related	3 times greater with Patch	
Allergy-related	>18 times greater with Patch	
Nerve system-related	5 times greater with Patch	
Psychiatrics	>30 times greater with Patch	
Cardiovascular, Respiratory, Musculoskeletal, General, Body as a whole	>8 times greater with Patch	

Data were extracted from the original article. The detailed data and percentage calculation for each category were not presented in the article.

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ON ORIGINAL

Post-Market AE Reports On The 2-mg and 4-mg Nicotine Lozenge from UK

The sponsor provided the 3-month spontaneous AE reports for nicotine lozenge marked in UK in response to Agency's Comment #4 -- *Provide adverse event reports from countries already marketing the lozenge over-the-counter, behind the counter, or by prescription.*

The nicotine lozenge 2 mg and 4-mg has been marketed in the UK since October 1, 2001 and France since December 19, 2001. The sales units and spontaneous adverse event (AE) reports that the sponsor collected up to January 27, 2002 (for UK) and February 15, 2002 (for France) are summarized in ***Tables 10 and 11***. The dosing regimens were different from the proposed one for the US marketing; the maximal dose was up to 15 lozenge per day for UK marketing, but up to 20 lozenge per day was in the proposed labeling for the US marketing.

Table 10. AE reports for Nicotine Lozenge marketed in UK and France

Country & Marketing Period	Sales Units	Total Case Reports	Total AE Reports
UK (1st Oct 01 – 27th Jan 02)	[redacted]	102	256
	4-mg: 70%		
	2-mg: 30%		
France (17th Dec 01 – 15th Feb 02)	[redacted]	1	1
	4-mg: 57%		
	2-mg: 43%		

There were no serious AE reports associated with nicotine lozenge. The general spectrum of AEs associated with nicotine lozenges appears similar to that from the previous clinical trial submitted in the original NDA, as seen in ***Table 12***. However, the following AEs that were highlighted in the spontaneous reports: paresthesia (skin, mucosa and circumoral), dizziness, palpitation, syncope and chest pain. These AEs were not indicated in the primary clinical review of the clinical safety trial in the original NDA submission, probably due to 5% cut-off for the AE reports in the clinical trial. The 4-mg nicotine lozenge users apparently experienced more AEs than the 2-mg nicotine lozenge users after distribution adjustment on both dosage forms.

It is difficult to perform a comparison between the 2 dosage forms, and between these AE reports and the previous clinical trials because the AE incidence rates from the spontaneous reports can not be determined. However, these AE reports may suggest that the 4-mg nicotine lozenge potentially causes more toxicity on cardiovascular and central/peripheral nerve systems of smokers, particularly those with compromised cardiovascular functions.

Table 11. The 3-Month Spontaneous Postmarketing AE Reports for Nicotine Lozenges in the UK

Body System	AEs		Nicotine Lozenge Strength (*No. of Users*)		
	Type	No.	2-mg	4-mg	Unknown
Gastrointestinal System (Total AEs: 117)	Nausea	26	4	34	3
	Vomiting	12			
	Hiccup	10			
	Heartburn	9			
	Dyspepsia	8			
	Flatulence	8			
	Glossitis	8			
	Dysphagia	7			
	Abdominal pain	5			
	Diarrhea	4			
	Constipation	2			
	Others	18			
Cardiovascular System (Total AEs: 14)	Palpitation	5	1	3	
	Chest Pain	5	0	5	
	Syncope	4	2	1	
Center/Peripheral Nerve System (Total AEs: 41)	Paresthesia	23	3	18	2
	Dizziness	7			
	Dystonia	4			
	Tremor	4			
	Headache	2			
	Sweating	3			
	Flushing	3			
Respiratory System (Total AEs: 34)	Pharyngitis	19	2	12	
	Coughing	6			
	Dyspnea	4			
	Others	5			
Body as a Whole (Total AEs: 16)	Malaise	7	1	6	
	Injury	5			
	Influenza-like Symptoms	2			
	Pain	2			
	Others	2			
All System	All AEs	256	13	79	5

The data are extracted and summarized from sponsor's spread data sheet of individual case reports "Body System Tabulation/Adverse Experience Report" and the brief response to the Agency comment #4.

Table 12. Summary of Efficacy and Safety for Nicotine Lozenge from Previous Clinical Trial submitted in the original NDA (Study S1410043)

Outcomes	2-mg Nicotine Lozenge			4-mg Nicotine Lozenge		
	Active n=459	Placebo N=458	Active> Placebo	Active n=450	Placebo N=451	Active> Placebo
Continuous Quit Rate (% Subjects)†						
6-week	46	30	16	49	21	28
3-month	34	22	12	35	14	21
6-month	24	14	10	24	10	14
Most Common Treatment Emergent AEs (>5% Subjects)‡						
Headache	5	6	-1	8	3	5
Diarrhea	4	2	2	5	4	1
Flatulence	9	7	2	8	5	3
Heartburn	5	2	3	6	<1	5
Hiccup	3	0	3	6	0	6
Nausea	12	5	7	15	5	10
Coughing	4	3	1	6	3	3
Sore Throat	3	3	0	5	4	1
URTI	12	10	2	10	6	4

Data were extracted from the primary clinical review (by Dr. Harold Blatt) and the secondary clinical review (by Dr. Celia Winchell) for the original NDA submission.

† **Continuous quit rate** was defined as % of subjects with self-reported abstinence from smoking from the end of week 2 to the end of week 6, month 3 and month 6.

‡ **AE rates** with more than 5% were reported.

Conclusion and Comments (for safety evaluation)

1. Cardiovascular safety evaluation for nicotine patches from 3 literature reports showed that the continuing nicotine exposure for 3 days from nicotine patch in smokers with coronary artery disease had no significant cardiac toxicity. This might be a valuable reference for risk assessment of the nicotine lozenge. However, the 4-mg nicotine lozenge has the higher Cmax and faster nicotine delivery (shorter Tmax) than nicotine patch at multiple dosing regimen, and daily systemic nicotine exposure for the lozenge is still unknown. The acute cardiac effects of rapid higher nicotine loading from the 4-mg nicotine lozenge can not be assessed from these literature reports. The phase IV clinical safety study on the 4-mg nicotine lozenge and 4-mg gum in smokers with medical conditions, as recommended by the Agency in the previous review cycle, may provide supportive evidence for justification.

2. The 10-year post-market AE reports on Rx nicotine gum and Rx nicotine patch retrieved from the FDA spontaneous AE report database (from 1984-1994) showed no serious adverse events associated with both products. More AEs in all categories were reported from the nicotine patch than from the nicotine gum. This may suggest the continuing nicotine exposure from the patch may only develop a limited tolerance to nicotine on certain pharmacological effects, and thus caused more AEs than the intermittent nicotine exposure from lozenge and gum.

3. The 3-month post-market AE reports from the UK showed no serious adverse events associated with both dosage forms (2-mg and 4-mg) of nicotine lozenge. The general spectrum of AEs associated with nicotine lozenges appears similar to that from the previous clinical trial submitted in the original NDA. The more 4-mg nicotine lozenge users experienced more adverse events than then 2-mg lozenge after adjusted with distribution of each dosage form, particularly paresthesia (skin, mucosa and circumoral), dizziness, palpitation, syncope and chest pain. This may suggest that the 4-mg nicotine lozenge could more potentially impact on cardiovascular and central/peripheral nerve systems of smokers, particularly those with compromised cardiovascular functions.

VIII. Dosing, Regimen, and Administration Issues

There was a dosing regimen issue raised in the previous review cycle, as indicated in the approvable letter of October 19, 2001, which was the inconsistency of the dosing regimen in the proposed labeling with that used in the clinical efficacy study. The proposed dosing regimen in the labeling was [redacted] -2 hours up [redacted] /day for the first 6 weeks, however, the dosing regimen evaluated in the single efficacy trial (in original NDA submission) was q1-2 hours up to 20 lozenges/day for the first 6 weeks. The sponsor did not have additional efficacy data in the previous and current submissions to support the effectiveness of the proposed dosing regimen, but the updated labeling was submitted and is being reviewed by IDS (HFD-560). Refer to labeling review for the labeling resubmission.

IX. Use in Special Populations

1. Gender Differences

No new information was provided in the resubmission to evaluate safety and efficacy of nicotine lozenges based on gender. Clinical trial (S1410043) submitted in the original NDA found that female subjects experienced more AEs and showed lower smoking cessation rates than male subjects for both 2-mg and 4-mg nicotine lozenges. Refer to the primary clinical review and the secondary clinical review for the original NDA.

2. Age differences

No new information was provided in this resubmission to evaluate different effects of the nicotine lozenge in elderly and pediatric (teenager) populations. The clinical trial (S1410043) submitted in the original NDA showed a slightly higher AE incidence in subjects over 55 years old compared to those under 55.

3. Ethic/racial Differences

No clinical studies in the previous and current submissions were conducted to address potential difference in nicotinic effects (efficacy and safety) among different ethic populations. The sponsor noted in this resubmission from literature reports that certain populations, such as Asians, metabolize nicotine more slowly than Caucasians, Hispanics, and African-Americans due to polymorphism of CYP2A6 (a major enzyme for nicotine metabolism). No studies have been conducted to evaluate safety and efficacy of the nicotine lozenge in different ethic populations. In the previous clinical trial submitted with the original NDA, 94% of subjects were Caucasians.

4. Populations with certain medical conditions

No clinical studies in the previous and current submission were conducted for safety evaluation of nicotine lozenges in subjects with cardiovascular disease, diabetics, renal disorder, or hepatic impairment. In this resubmission, the sponsor cited three clinical studies from the literature and showed that nicotine patches (15-mg, 21-mg) did not induce significant cardiac toxicity in smokers with coronary artery disease with and without concurrent cigarette smoking. The sponsor has committed to conduct a phase IV study to evaluate safety of the 4-mg nicotine lozenge in smokers with cardiovascular disorders and diabetics. The study protocol was submitted and is being reviewed by Dr. Linda Hu (HFD-560).

5. Pregnancy and lactation population

No clinical studies were conducted in subjects with pregnancy or breast-feeding in the previous and current submission. A literature review regarding reproductive toxicity of nicotine was submitted in the original NDA and reviewed by a pharm/tox reviewer in HFD-170 in February 20, 2001. Animal studies suggest that nicotine has toxic effects on fetal and neonatal development. The human experience should be collected from marketed NRT products. However, this issue impacts whole class of NRT products. For this product, appropriate "Warning" should be included in the labeling.

6. Abuse liability in Teens and Adults

The clinical abuse liability study of nicotine lozenge in teenage and adults submitted with the original NDA was reviewed by Dr. Cynthia McCormick. It was concluded that there was no significant signal regarding the abuse potential of

this product by itself or compared with the currently marketed OTC product, Nicorette gum.

X. Conclusions and Recommendations

Conclusion

Taken together with results from previous clinical trials, the following conclusions could be drawn form the literature information provided in this NDA resubmission. The supportive evidence is expected from the committed phase IV clinical safety study on the 4-mg lozenge and the 4-mg gum.

1. The maximal plasma nicotine level achieved by the 4-mg nicotine lozenge seems to be comparable to the currently marketed OTC 4-mg nicotine gum at single and multiple dosing regimens, and comparable to the currently marketed OTC 21-mg nicotine patch at single dosing regimen.

2. The 4-mg nicotine lozenge at single and multiple dosing regimens appears to produce slightly higher total systemic nicotine exposure (AUC) than, but may be comparable to, the currently marketed OTC products, 4-mg nicotine gum and nicotine patches.

3. Post-marketing experience on the nicotine lozenge from the UK showed no serious adverse events associated with the nicotine lozenge (2-mg and 4-mg) in the 3-month spontaneous post-market report period.

4. Post-marketing experience on the nicotine patch and gum for prescription use showed no serious adverse events associated with both products in the 10-years spontaneous post-market report period (1984-1994).

5. Cigarette smoking produces the highest systemic nicotine exposure as compared with all nicotine replacement therapy products, including the 4-mg nicotine lozenge, at single and multiple dosing regimens.

6. The flat dose-response for certain effects on cardiovascular system, one of major targets of nicotine, may to some degree "buffer" effects of the slightly increased nicotine bioavailability from the 4-mg lozenge.

Recommendation

The recommendation for this NDA is approval for OTC marketing. The sponsor has committed to conduct two phase VI studies; and the study protocols have been reviewed by Dr. Linda Hu (HFD-560). There are no additional comments and recommendations on the phase IV study designs.

XI. Appendix: **Bibliography**

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