Overall Adverse Events

Sources of adverse events included both questionaires and spontaneous reports. Including all sources, nearly 4700 adverse events were recorded during this study. This included about 2900 reports by 111 subjects on active drug and about 1800 reports by 107 subjects on placebo. For subjects on both treatments, about 1/3 of adverse events were spontaneously reported and 2/3 were elicited in response to directed questioning. Inspection of the data set revealed that response to directed questioning was unable to distinguish between active and placebo medication in a way that would be meaningful to physicians and patients using this product (everyone complained about everything). Spontaneous adverse events were primarily of 5 types: local events related to the irritant effects of the drug and the dosage form (irritation of the throat, mouth or lips, coughing), possible nicotinic effects (eg dyspepsia), events consistent with withdrawal or drug dependence (restlessness, etc), events likely to be related to the long term effects of smoking (bronchitis etc), and events of unknown significance, probably unrelated to drug use (headaches, flu etc).

Local irritant effects inlcuded irritation to the throat, mouth, tongue or lips. Other local effects included coughing, rhinitis and pain in the jaw or neck.

Dyspepsia was the most prominent of the nicotinic effects, with hiccup notably absent in placebo but reported by 5 subjects on active drug. Palpitations or tachycardia were reported by 1 subject on each treatment.

Withdrawal symptoms were reported by slightly more subjects on active than placebo.

The number of subjects reporting a given adverse event is given in the following tables based on the reviewer's assessment of the type of event.

Possible Local Effects

Adverse Event	Active	Placebo
IRRITATION LOCAL	73	46
COUGHING	35	9
RHINITIS	33	13
PAIN JAW/NECK	10	6
SINUSITIS	7	9
TASTE COMMENTS	5	13
TOOTH DISORDER	5	6
DYSPHONIA	2	0
PRACTICAL PROBLEMS	2	1
ASTHMA	1	1
BRONCHOSPASM	1	0
CONJUNCTIVITIS	1	2
SALIVA INCREASED	1	2
PAROSMIA	0	1

Table made by the reviewer based on recoding of the sponsor's electronic data set.

Possibe Nicotinic Effects

Adverse Event	Active	Placebo
DYSPEPSIA	22	10
DIARRHOEA	8	3
NAUSEA	6	6
HICCUP	5	0
SWEATING INCREASED	2	0
PALPITATION	1	0
TACHYCARDIA	0	1

Table made by the reviewer based on recoding of the sponsor's electronic data set.

Possible Nicotine Withdrawal

Adverse Event	Active	Placebo
ANXIETY	12	8
DIZZINESS	12	8
MYALGIA	7	3
DEPRESSION	5	2
DRUG DEPENDENCE	5	2
FATIGUE	4	1
IRRITABILITY	4	0
SLEEP DISORDER	4	4
CONCENTRATION IMPAIRED	3	5
EMOTIONAL LABILITY	3	0
WITHDRAWAL SYNDROME	3	3
APPETITE INCREASED	2	0
SOMNOLENCE	2	1
AGITATION	1	2
APATHY	1	1
TREMOR	1	0
CONFUSION	0	3

Table made by the reviewer based on recoding of the sponsor's electronic data set.

Possible Smoking Related Disorders

Adverse Event	Active	Placebo
CHEST DISCOMFORT	8	4
BRONCHITIS	4	2
DYSPNOEA	2	0
HYPERTENSION	1	0
SPUTUM INCREASED	1	0

Table made by the reviewer based on recoding of the sponsor's electronic data set.

Possibly Unrelated Events

Adverse Events	Active	Placebo
HEADACHE	38	22
PAIN	13	11
PAIN BACK	12	2
ALLERGY	11	8
PARAESTHESIA	6	0
INFLUENZA-LIKE SYMPTOMS	5	6
PRURITUS	5	0
CONSTIPATION	4	4
FLATULENCE	4	2
INSUFFICIENT INFO.	4	7
FEVER	3	0
MENSTRUAL DISORDER	3	0
THIRST	3	0
ABDOMINAL PAIN	2	4
ACCIDENT	2	0
ACNE	2	1
BURSITIS	2	0
EDEMA	2	0
FLUSHING	2	2
INFECTION	2	3
MALAISE	2	0
NEPHRITIS INTERSTITIAL	2	0
PAIN MOUTH	2	2
POLYURIA	2	0
URINARY TRACT INFECTION	2	1
ARTHRITIS	1	1
ASTHENIA	1	1
DYSMENORRHOEA	1	0
EAR DISORDER	1	2
EPISTAXIS	1	2
GOUT	1	0
GUM HYPERPLASIA	1	1
HEPATITIS	1	0
HERPES SIMPLEX	1	0
INFECTION VIRAL	1	0
LYMPHADENOPATHY	1	1
MUSCLE WEAKNESS	1	0
OEDEMA	1	0
OEDEMA GENERALISED	1	0
PREMENSTRUAL TENSION	1	0
RASH	1	0
RIGORS	1	0
SKIN DISORDER	1	0
UPPER RESP TRACT INFECTION	1	1
VERTIGO	1	0
WEIGHT DECREASE	1	0
ANOREXIA	0	1
ARTHRALGIA	0	1
CRAMPS LEGS	0	1
CYSTITIS	0	1
GLAUCOMA	0	1
LEG PAIN	0	2
MYDRIASIS	0	1
OEDEMA LEGS	0	1
VISION ABNORMAL	0	1

Table made by the reviewer based on recoding of the sponsor's electronic data set.

A total of 7 subjects in this study (5 on active medication, 2 on placebo) reported symptoms of possible drug dependence. The experiences of these subjects are described below.

Subjects reporting possible drug dependence

Subject	Event	Outcome	Last Drug Dispensed
placebo 57 yo M, FTQ=8, 35cig/day	ineffective and no satisfaction day 2	Failure	Study Start
placebo 53 yo F, FTQ=7, 20 cig/day	satisfaction level down and craving day 7	Failure	Day 7
active 52 yo F, FTQ=7, 20 cig/day	drug dependence day 180; malaise, fatigue day 14, 21	6 week Success	Day 90
active 66 yo F, FTQ=6, 18 cig/day	increased appetite, difficulty concentrating, headache, craving, drug dependence day 180. No other ae's reported during trial.	6 week Success	Day 90
active 48 yo M, FTQ=10, 60 cig/day	Drug dependence (inhaler) reported at 180 days. No other WD reported.	6 week Success	Day 90
active 40 yo M, FTQ=3, 13 cig/day	Drug dependence (inhaler) reported at day 180. Stress reported days 180, 365. No other WD.	Failure	Day 90
active 25 yo F, FTQ=9, 35 cig/day	Drug dependence (inhaler) reported day 180. Reported crying for no reason day 7	Failure	Day 90

Among subjects on placebo, reports possibly involving drug dependence occur early in the trial and (correctly) involve the subect's observation that there is no therapeutic benefit from the inhaler. Among subjects on active drug the situation is quite different. Reports of dependence refer to the inhaler itself and they emerge in all cases at the first visit after the last day the drug has been stopped. Interestingly, subjects who report dependence do not seem to have previously reported a lot of withdrawal, nor have they been able to stop smoking.

This data suggests that subjects on active drug may have experienced withdrawal at the time that tapering of the inhalers began. This is explored in the following table:

Number of subjects reporting withdrawal symptoms by treatment group and 6 week outcome

	2	7	14	21	42	90	180	365
Active Fail	9	10	9	7	3	0	3	1
Active Quit	7	4	5	3	3	1	9	6
Placebo Fail	17	15	7	3	1	0	0	0
Placebo Quit	0	0	0	1	1	1	2	2

Early in this study, placebo quitters had the fewest spontaneously reported withdrawal events during the first weeks of the trial, while failures had the most withdrawal. It is notable that among the active quitters, there is a re-emergence of withdrawal symptoms following day 90 (the last day drug was available for dispensing in this trial).

Local Effects

Subjects were asked about the occurrence of adverse events with open ended questions followed by mild, moderate or severe ratings. There was a higher incidence of Irritation in Mouth and Throat (at 2 and 7 days), and Coughing (at 2 days) on active drug as presented in the following tables.

Irritation in Mouth and Throat

Day	2	7	14	21
Active N at visit	**108**	**102**	**89**	**87**
# Reporting Irr (% of N at visit)	33 (31)	16 (16)	14 (16)	8 (9)
Mean severity	1.1	1.2	1.3	1.3
Placebo N at Visit	**100**	**84**	**63**	**45**
# Reporting Irr (% of N at visit)	10 (10)	10 (12)	8 (13)	2 (4)
Mean severity (SEM)	1	1.1	1	1
*P-value	<.0005	-	-	-

*P-value is based on Pearson chi-square test . The N at visit and p values are from Table 15 of the final study report, severity from summary report. All subjects did not report the severity.

Coughing

Active # Coughing (% at N at visit)	21(19)	16 (16)	11 (12)	10 (11)
Mean severity	1.2	1.6	1.3	1.1
Placebo # reporting cough (%)	4 (4)	4 (5)	3 (5)	1 (2)
Mean Severity	1.3	1.3	1.5	1
*P-value	.001	.017		

*P-value is based on Pearson chi-square test . The N at visit and p values are from Table 15 of the final study report, severity from summary report. All subjects did not report the severity.

Success, Failure and Dropouts

The success, failure, and dropout table below shows higher numbers of successes for active and higher failure rates for placebo at each visit as would be expected from an efficacious product. . In the following table, success + failure + dropout = N (111 in active and placebo). *Unlike the Schneider study where dropsouts were higher in active at day 2, the dropout rate for placebo is higher at each visit.*

Success, Failure and Dropouts

Day	**2**	**7**	**14**	**21**	**42**	**90**	**180**
Active							
(N=111)							
Successes				62	50	34	22
Failures				30	34	45	50
Dropout	3	9	13	19	27	32	39
% Dropouts	2.7	8.1	11.7	17.1	24.3	28.8	35.1
Placebo							
(N=111)							
Successes				21	15	9	7
Failures				21	15	9	7
Dropout	9	25	43	52	58	65	68
% Dropout	8.1	22.5	38.7	46.8	52.3	58.6	61.3

This is the sponsors classification, values are from the sponsor's summary.
Successes = Known to have been abstinent since the week 2 visit through the indicated week visit
Failures = Known not to have been abstinent since the week 2 visit through the indicated week visit.
Dropouts = The remainder.

Reasons for Dropout

Reasons for dropouts are shown in the following table. The most notable difference is that dislike of the medication is higher in the placebo group consistent with their finding that patient acceptance of the study drug is good. After the first visits, dropout for adverse events is higher in the placebo group.

Reasons for Dropout

Days	2	7	14	21	42	90	180	365
Active (N=111)								
Dropout	3	9	13	19	27	32	39	43
Reason for dropout								
Non-compliance	0	1	4	5	6	6	8	8
Adverse experience	2	5	6	7	9	9	10	11
Lost to follow-up	0	0	0	3	5	8	12	15
Did not like medication	0	0	0	1	3	5	5	5
Illness or accident	0	0	0	0	0	0	0	0
Other reasons	1	3	3	3	4	4	4	4
Placebo (N=111)								
Dropout	9	25	43	52	58	65	68	69
Reason for dropout								
Non-compliance	1	6	6	7	7	9	9	10
Adverse experience	1	5	11	14	16	16	17	17
Lost to follow-up	1	1	4	5	8	11	13	13
Did not like medication	5	8	14	17	18	20	20	20
Illness or accident	0	1	1	1	1	1	1	1
Other reasons	1	4	7	8	8	8	8	8

Table from the sponsor's summary report

Withdrawals due to Adverse Events

Twenty-nine (29) subjects were withdrawn from the study due to adverse events, eleven on active treatment and eighteen on placebo. None of these adverse events were considered serious. Six of the 11 active subjects and 9 of the 18 placebo were withdrawn secondary to cough or mouth /throat irritation related symptoms.

Subjects on Active Drug Withdrawn due to Adverse Events

Subject No. Active	Week/day	Adverse Event (AE)
	6	Stress, work problems, bronchitis
	2	Light headedness, general weakness, nausea, sore throat, (menthol irritation), stomach ache
	day 2.	Throat irritation, dizzy spells
	day 2	Anxiety, nervousness, paranoia
	26	Headache, concentration, eating more (craving)
	6	Heartburn
	1	Coughing
	1	Headache, coughing
	3	Throat irritation, coughing, allergy, hoarse voice
	1	Excess saliva, diarrhoea
	52	Lost job, stress, headache, gas

Table fro the sponsor's summary

Withdrawals due to Adverse Events

Subjects on Placebo Withdrawn due to Adverse Events

Subject No. Placebo	Week/day	Adverse Event (AE)
	2	Headache
	3	Headache
	1	Disorientation
	26	Oedematous mouth, respiratory tract infection
	2	Menthol irritation, sore throat
	2	Reduced concentration ability, irregularity, diarrhoea
	2	Weight gain, coughing
	2	Cool numbing sensation at the top of the throat
	6	Dry mouth, bad taste
	day 2	Tightness in chest, chest pain
	1	Blood pressure, anxiety, inability to concentrate
	2	Nausea, ear infection, coughing, cold and flu sx, menthol irritation
	1	Illness or accident unrelated to the inhaler
	1	General weakness
	3	Constipation, gas, leg symptoms, bad taste
	6	Ulcer on tongue
	1	Scratchy throat
	3	Anxiety, tightness in chest

Table from the sponsor's summary

Discontinuation of Treatment due to Adverse Events

Thirty-two subjects permanently discontinued their treatment, 16 on active treatment and 16 on placebo. These are described in the following tables. Only two on active drug discontinued due to sore throat and none due to cough; discontinuation due to local effects was not more common in the active group. None of these adverse events were considered serious. One patient on active drug felt that she was becoming addicted to inhaler.

Active Drug Permanent Discontinuation of Treatment

Subject No. **Active**	Week/day	Event
	26	Sore throat
	12	Nervousness
	26	Gagging, dizziness
	3	Strong taste
	3	Job stress, strong taste
	day 2	Anxiety, nervousness, paranoia
	12	Death in family
	12	Stress
	6	Heartburn
	26	Stomach upset
	12	Stress
	2	Throat irritation
	26	Felt that she was getting addicted to inhaler
	6	Stress
	3	Sore throat
	6	Stress, problems

Table from the sponsor's summary report

Placebo Drug Permanent Discontinuation of Treatment

As in the active group, two subjects discontinued due to the unpleasant taste and two due to throat symptoms. Mouth sores and mouth ulcers are also listed in the placebo group.

Placebo Group Permanent Discontinuation

Subject No. Placebo	Week/day	Event
	1	Headache
	1	Stress
	6	Does not like menthol
	26	Stress
	1	Disorientation
	26	Sleep disturbances
	6	Canker sores, mouth tender
	2	Weight gain
	2	Cool numbing throat
	6	Bad taste
	1	Bad taste, dizziness
	2	Menthol irritating
	6	Ulcer on tongue
	3	Traumatic family experience
	1	Scratchy throat, nuisance at work
	2	Depression

Table from the sponsor's summary report

SAFETY SUMMARY

Only 1 serious adverse event occurred and it was not considered related to the study drug. There was a higher incidence of local effects (Irritation in Mouth and Throat and Cough) in the active group at the beginning of therapy

DISCUSSION

The efficacy is in this study is very similar to the efficacy demonstrated in the Schneider study; both studies show substantial evidence of efficacy. This is a population of relatively light smokers (CO < 10 at baseline in 7 active and 6 control) but the product shows significant evidence of efficacy even after these subjects are excluded. These later studies show far better efficacy than the first studies of this product, probably related to the higher dose.

There are few differences in this study compared to the Schneider study. This study had more subjects with baseline medical conditions (88 vs 69 %) and more subjects on baseline medication (69 vs 40 %). This study reported less craving at 7 and 14 days; the Schneider study did not.

Serious adverse events were infrequent in this trial, the only one listed was chest pain and there is no mention of any cardiac event in the subsequent hospitalization. It is evident that the investigator did not consider the event related, for the subject was continued in the trial.

CONCLUSION:

The Nicotine Inhaler treatment showed substantial efficacy as compared to placebo in this trial. As in the Schneider study, mouth and throat irritation and cough were more frequent on active drug in the first week of treatment. No severe or unexpected adverse effects related to this therapy were identified.

AW Longmire

AW Longmire MD
Medical Review Officer

E. Douglas Kramer 11-6-96

E D Kramer MD
Peer Review

NDA 20-714

cc:
Orig. NDA 20-714
Div. File
HFD-170/Kramer/Chang Li/Ross/Doddapaneni/Geyer/Permutt/McNeal
HFD-344

Medical Review

Sponsor	Pharmacia
Drug	Nicotine Inhaler
Received	May 3,1996
Reviewer	AW Longmire
Peer	ED Kramer
Study	6, CTN: 92NNIN003
Investigator	Nina G. Schneider, Ph.D.
Location	Nicotine Dependence Research Unit VA Medical Center, Brentwood, Los Angeles, CA, USA

Title: The Nicotine Inhaler in Smoking Cessation.
A Double-Blind Placebo-Controlled Clinical Evaluation.

ABSTRACT:

This was a double-blind placebo controlled single center trial of the Nicotine Inhaler for smoking cessation in 223 smoking adults aged 21 and older. The dose was self titrated between 4 to 20 inhalers per day for up to 6 months. Self reported rates of complete abstinence from week 2 through 1 year were verified by CO-levels < 10 ppm. The Nicotine Inhaler treatment showed significant higher complete abstinence rate at 6 weeks, 3 months, and 6 months ($p = .049$ at 6 months) as compared to placebo:

at 6 weeks	44% vs 23%
at 3 months	32% vs 15%
at 6 months	21% vs 11%
at 12 months	13% vs 10%.

Throat and mouth irritation and cough were higher on active drug in the first weeks of treatment but no serious or unexpected adverse effects of this therapy were identified.

The tested device is different from the device intended for marketing. This is addressed in appendix A; the two devises are considered functionally equivalent.

STUDY DESCRIPTION:

Subjects: Subjects were men and women over 21 years old, who had been smoking ≥ 10 cigarettes per day for ≥ 3 years and motivated to quit smoking. They were recruited by newspaper ads and television notices or were referred to the clinic. Members of the same household or close friends of participants and patients with diabetes and symptomatic cardiovascular were excluded. The number of subjects required was calculated from previous studies of nicotine replacement therapy and designed to detect a difference in active and placebo rates of 30 % vs. 15% at 6 weeks with 80 % power and alpha = 0.05 using a one-tailed test. The required number of subjects was 188 and it was decided to randomise 220 to allow for treatment withdrawal and protocol violators.

Treatment: The treatment was Nicotine Inhaler or Placebo Inhaler at self-titrated doses. The Nicotine inhaler contained 10 mg nicotine and 1 mg menthol and would release about 4 mg of nicotine (buccal absorption or swallowed, 50 % bioavailable) with 80 deep inhalations over 20 minutes. The bioavailable nicotine is between that of the 4 mg and 2 mg gum. The placebo contained menthol.

Subjects were instructed to use the inhaler on an ad libitum basis from 4 up to 20 ~~in~~halers per day for at least 6 weeks (recommended as frequently as possible the first week) and for 3 month if necessary. After 3 months the number of inhalers were tapered for up to 6 months with no treatment allowed after 6 months. Follow-up was scheduled for 12 months. The subjects had an instructional video and written instructions at entry and 30 minute individual counselling sessions at week 1, 2, 3, and 6. Group therapy was not given.

Study visits: Subjects who answered the ads were called to the clinic and screened for possible eligibility about 4 weeks before Quit-Day. The subsequent visits were as follows:

(Visit 0) (Baseline 2 weeks before Quit-Day) for completion of history and questionnaires and measures of CO, cotinine, VS, weight, EKG, final screening and instructions.
(Visit 1) (Randomisation, Day before Quit-Day) for further training, test dose, issuing supplies, CO, diary, weight, and scheduling.

QUIT day 0

(Visit 2) 1-2 days CO, cotinine, diary and weight at this and all following visits.
(Visit 3) 1 week
(Visit 4) 2 weeks
(Visit 5) 3 weeks
(Visit 6) 6 weeks
(Visit 7) 3 months
(Visit 8) 6 months
(Visit 9) 12 months

Primary outcome: Success was complete abstinence (no "slips" allowed) for at least 4 weeks from week 2 to week 6, confirmed by exhaled CO < 10 ppm. This is the usual standard of efficacy for cessation products. Failure was assumed if the subject dropped out or reported any use of cigarettes.

Secondary outcome: Assessments of subjective parameters such as withdrawal symptoms, acceptability and self-perceived helpfulness.

Safety outcome: Events were tabulated from open-ended questions and a 19 item Withdrawal Symptom Questionnaire at each visit

Usage assessment: Daily use of inhalers were recorded in a diary through 6 weeks and subjects were also asked to estimate their remaining stock of unused inhalers and count used and un-used inhalers at each follow-up visit through 6 months.

Statistical analyses: Subjects were randomised at Visit 1, day before Quit-Day. Subjects were included in the analysis if they were given medication at Visit 1. An early report was performed at 3 months without disclosing the individual treatment code. The quit rates were calculated by chi square with continuity correction.

RESULTS:

Subjects: All subjects recruited by newspaper and television notices between November 1992 and March 1993, were screened for inclusion in the trial. In order to achieve a minimum of 220 randomised subjects, 285 subjects were seen for the baseline visit. Of these, 223 were eligible and willing to participate in the trial. At visit 1, they attended the first session and were randomised and assigned subject numbers. All 223 subjects were included in the safety database and the efficacy analysis.

Demographics: The demographics of the subjects randomised to treatment are given in the following table. The groups are generally well matched.

Subjects Characteristics at Baseline - Demographics

	Active (N=112) Mean (SD) (low-high)	**Placebo (N=111) Mean (SD) (low-high)**	**P- value**
% Female	35.7	37.8	.85
% White	89.3	77.5	.03
% Black	7.1	10.8	.47
Age	44.1 (11.3) (22-71)	44.9 (10.8) (26-74)	.67
Weight (kg)	77.2 (16.1) (42-123)	79.2 (16.8) (42-145)	.36
Cig /day	29.2 (11.3) (10-60)	26.2 (9.8) (12-70)	.04
CO	25.5 (9.5) (10-59)	25.7 (9.2) (7-57)	.87
FTQ	7.5 (1.5) (3-10)	7.2 (1.8) (3-1)	.32

The table values are supplied by the sponsor. P-values are from 2-sided unpaired t-test or Pearson's chi-square with continuity correction when applicable. The # cig/day, CO (This was from visit 0), age, and FTC, were verified by electronic data.

Although subjects were excluded for diabetes and symptomatic cardiovascular disease, approximately half of the participates had medical problems and /or were taking medication at baseline as depicted on the following two tables. Not demonstrated here is that the population included patients that underwent surgery and patients with carcinoma and AIDS. This is apparent in the serious, unrelated adverse events on a later table.

Current Medical Problems at Baseline

Category	# of reported medical problems (# subj. reporting) Active(N=112)	Placebo (N-111)	Total
Pulmonary	5 (5)	6 (6)	11 (11)
Cardiovascular	13 (10)	11 (9)	24 (19)
Gastrointestinal	6 (6)	8 (6)	14 (12)
Metabolic/Endocrine	6 (6)	10 (9)	16 (15)
Musculo-Skeletal	18 (17)	14 (13)	32 (30)
Allergic	7 (7)	9 (9)	16 (16)
Miscellaneous	37 (31)	48 (41)	85 (72)
Total	92 (53)	106 (58)	198 (111)

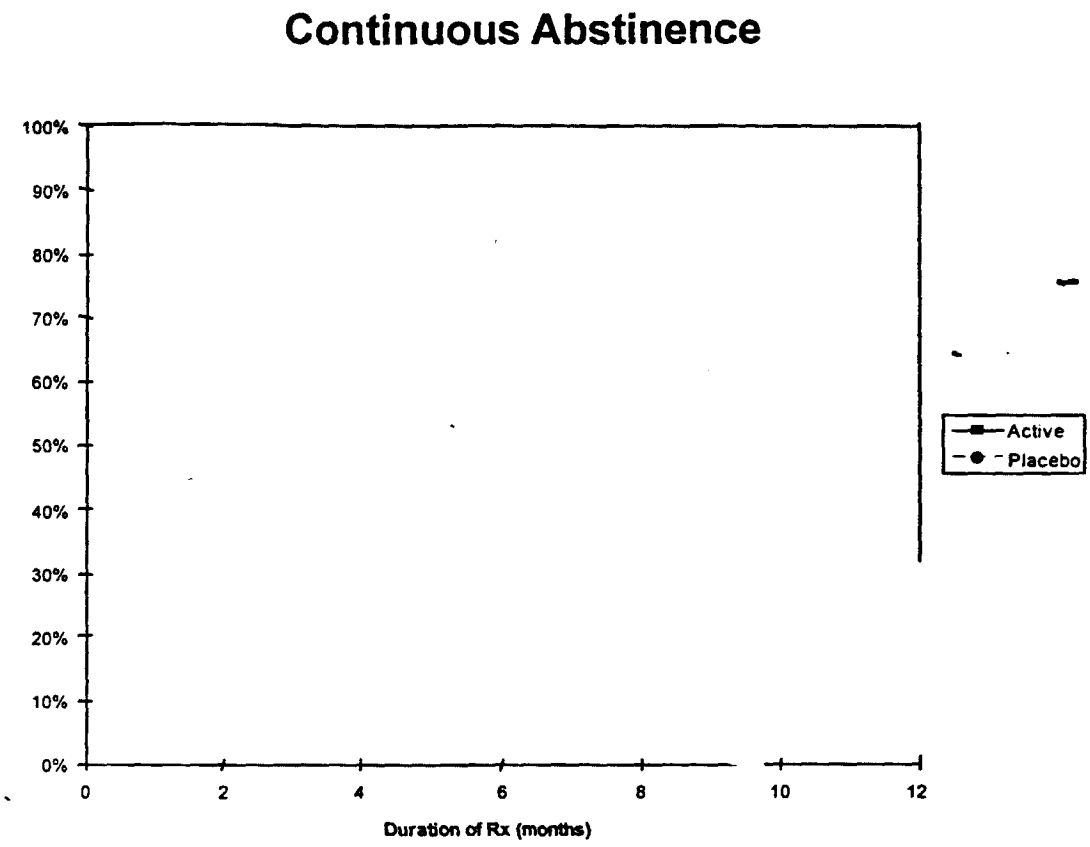
Table from the sponsor's summary report
Diabetic and symptomatic cardiovascular disease was excluded

TABLE 3
Current Medication at Baseline

Category	# of reported medications(# subj. reporting) Active(N=112)	Placebo(N-111)	Total
Pulmonary	0 (0)	0 (0)	0 (0)
Cardiovascular	9 (7)	7 (6)	16 (13)
Gastrointestinal	6 (5)	2 (1)	8 (6)
Metabolic/Endocrine*	6 (6)	8 (7)	14 (13)
Musculo-Skeletal	13 (11)	7 (7)	20 (18)
Allergic	1 (1)	2 (2)	3 (3)
Miscellaneous	44 (30)	60 (40)	104 (70)
Total	77 (42)	84 (49)	161 (91)

*Does not include diabetes.
Table from the sponsor's summary report

Primary Efficacy Analysis: The number and percentage of subjects completely abstinent from week 2 is shown in the following figure. Smoking cessation rates were significantly higher at 6 weeks, 3 months, and 6 months.



	Duration of Rx	6 weeks	3 months	6 months	12 months
Active N=112	# Quit Cigs	49	36	24	15
	% Quit Cigs	44%	32%	21%	13%
Placebo N =111	# Quit Cigs	26	17	12	11
	% Quit Cigs	23%	15%	11%	10%
	P value	0.005	0.002	0.049	0.547

Data display made from sponsor's electronic data set s6demo.xls. P-values are by chi-square with continuity correction. All subjects were treated for 6 weeks. Inhalattions were recommended at 4-20 Inhalers /day until 3 months but then were required to begin tapering and no inhaler use was allowed after 6 months.

Comments on the sponsor's classification of abstinence

The sponsor's classification of abstinence was based on 4 weeks of continuous self report of nonsmoking from week 2 to week 6 verified by an exhaled CO < 10. This definition meets the usual efficacy standard for these products. Review of the electronic data supplied by the sponsor revealed that among 6 week treatment successes in the active group, 14 subjects reported 1 or more slips during the first 2 weeks and 5 subjects had CO's > = 10 during this time. All active subjects classified as abstinent came to all visits in this period and all had CO verified abstinence at weeks 3 and 6. One of the above quitters began with a CO < 10 at baseline. Three placebo subjects reported lapses, 2 had missed visits and 2 had a CO>10 prior to week 2, but all were verified abstinent at weeks 3 and 6 by self report and CO. No subjects in either treatment group were incorrectly classified as failures. All subjects --regardless of treatment assignment -- recorded as abstinent for longer than 6 week had biochemical verification with no missed visits after week 6. The sponsor's classification of outcome is considered to be robust.

Secondary Outcome Analysis, Craving: Craving for cigarettes was assessed on a 5-point categorical scale: Not at all (0) - Markedly so (4). Differences in craving are shown in the following table:

	Craving			
Day	**Day before Quit**	**7**	**14**	**42**
Active (N-112)				
N	112	77	74	61
Mean Craving	2.36	1.79	1.7	1.34
Placebo (N=111)				
N	111	61	51	36
Mean Craving	2.49	1.93	1.51	1.06
P-value	0.334	0.484	0.355	0.174

From the sponsor's summary tables.
P-values from two-sided unpaired t-test.
Categories from not at all (0) to markedly /extremely so (4).

The craving data above is as supplied by the sponsor and does not show a decrease in craving.

SAFETY

Serious Adverse Events

Serious adverse events were far more common in this as compared to the other clinical studies. However, they were equally prevalent in active drug and placebo, and the list of adverse event as listed in the table below does not reveal any pattern of serious adverse event likely related to nicotine inhaler.

Serious Adverse Events

Subject No.	Date of study entry	Date of event	Diagnosis
Active			
	12-26-92	03-01-93	Shoulder surgery
	01-14-93	02-22-93	Foot surgery, left toe
	01-14-93	04-15-93	Foot surgery, right toe
	02-04-93	05-03-93	Kaposi's Sarcoma
	03-23-93	before 04-01-94	Terminal lung cancer
Placebo			
	08-12-92	03-03-93	Knee surgery
	08-12-92	10-08-93	Loss of hearing, tinnitus
	12-16-92	before 12-16-92	Terminal illness
	02-10-93	03-02-93	Bronchitis
	03-03-93	05-23-93	Diverticulitis
	03-03-93	05-13-93	Breast cancer
	03-03-93	01-07-94	Back surgery scoliosis
	03-31-93	06-27-93	Back pain, fall

* withdrawn from study

Table values supplied by sponsor

All Adverse Events

Sources of adverse events included both questionnaires and spontaneous reports. Including all sources, slightly more than 4300 adverse events were recorded during this study. This included about 2500 reports by 106 patients on active drug and about 1800 reports by 107 patients on placebo. For subjects on both treatments, about 1/3 of adverse events were spontaneously reported and 2/3 were elicited in response to directed questioning. Inspection of the data set revealed that response to directed questioning was unable to distinguish between active and placebo medication in a way that would be meaningful to physicians and patients using this product (everyone complained about everything). Spontaneous adverse events were primarily of 5 types: local events related to the irritant effects of the drug and the dosage form (irritation of the throat, mouth or lips, coughing), possible nicotinic effects (dyspepsia), events consistent with withdrawal or drug dependence (restlessness, etc), events likely to be related to the long term effects of smoking (bronchitis etc), and events of unknown significance, probably unrelated to drug use (headaches, flu etc). Common spontaneously reported nonserious events (5% or greater incidence) are listed in the following table. All events are summarized in the appendix.

Number of subjects spontaneously reporting adverse events

Recode of Sponsor's WHO Terms	Active N=112	Placebo N=111	Grand Total N=223
IRRITATION LOCAL	73	47	120
COUGHING	37	17	54
TASTE COMMENTS	27	18	45
RHINITIS	19	22	41
INFLUENZA-LIKE SYMPTOMS	20	14	34
HEADACHE	19	11	30
DIZZINESS WD	12	17	29
DYSPEPSIA	18	9	27
NAUSEA	13	11	24
SLEEP DISORDER WD	11	11	22
ANXIETY WD	11	7	18
PAIN BACK	6	8	14
TOOTH DISORDER	6	7	13
DIARRHOEA	7	5	12
DEPRESSION WD	7	4	11
WITHDRAWAL SYNDROME WD	7	4	11
HYPERTENSION	6	3	9
CONSTIPATION	4	5	9
CONCENTRATION IMPAIRED WD	3	6	9
IRRITABILITY WD	2	7	9
PAIN JAW/NECK	2	7	9
FATIGUE WD	7	1	8
PARAESTHESIA	7	1	8
CHEST DISCOMFORT	5	3	8
PRACTICAL PROBLEMS	2	6	8
SINUSITIS	4	3	7
BRONCHITIS	3	4	7
FLATULENCE	3	4	7
APPETITE INCREASED	2	5	7

Table made by the reviewer from the sponsorr's electronic data set.
WD = classified as possible withdrawal by reviewer

Note that while some likely nicotine withdrawal symptoms (eg irritability, impaired concentration) seem to be reported somewhat more frequently in placebo subjects others (eg anxiety) are reported with equal frequency between groups. Still other possible withdrawal symptoms (eg fatigue) are more common among subjects on active medication. The overall number of subjects reporting at least 1 possible withdrawal symptom is approximately the same between treatment groups. This could reflect either a subtle imbalance between treatment groups in their severity of dependence on nicotine at baseline (unlikely) or it could reflect the fact that more dependent smokers were able to quit on active drug (these subjects would be more likely to both experience withdrawal symptoms yet stay in the trial to report them).

A specific search for the terms bronchospasm and asthma found only 2 of bronchospasm, patient (day 7) and (day 365). These were both in the placebo group and were not on medication at baseline.

Drug Abuse and Dependence

A total of 6 subjects (2 on active medication and 4 on placebo) reported symptoms of possible drug dependence. These patients are described below:

Subject	Report	Outcome	Last drug dispensed
placebo, 38,M 30cig/day FTQ=6	Felt addicted to inhaler (day 7)	6 week success 1 year failure	Day 42
placebo, 65 M 20cig/day FTQ=6	Not strong enough (day 2)	6 week success 1 year failure	Day 21
active 36 M 20cig/day FTQ=7	Drinking a lot of alcohol (day 180)	6 week success 1 year failure	Day 90
placebo 63 F 20cig/day FTQ=7	Inhaler not helping (day 2)	6 week failure 1 year failure	Day 21
active 50 M 30cig/day FTQ=9	inhaler too weak (day 2)	6 week success 1 year failure	Day 90
placebo 49 M 20cig/day	Necessary to use inhaler constantly (day 2)	6 week success 1 year success	Day 21

Table made by the reviewer from the sponsorr's electronic data set.

Five of these reports occurred early in treatment, and 4 of those 5 were reports by subjects on placebo who believed (correctly) that their medication lacked effect. Of the 2 subjects on active drug who reported possible drug dependence, both had drug dispensed to them for the maximum length of time allowed and one of them reported excessive drinking at the visit following the last visit at which inhalers were dispensed. This difference suggested that some patients on active drug may have experienced withdrawal symptoms at the time that tapering of the inhalers began. This is explored in the following table.

Number of Patients reporting possible withdrawal symptoms by study day by 6 week outcome

Day of Study	0	2	7	14	21	42	90	180	365
Active Failures	0	16	6	4	2	4	2	0	0
Active Successes	1	10	7	4	4	8	3	8	7
Placebo Failures	0	22	6	5	2	2	0	0	0
Placebo Successes	1	7	5	3	4	3	1	0	0

Table made by the reviewer from the sponsor's electronic data set. 49 active and 26 placebo subjects were successfully abstinent at week 6.

This data suggests that successful quitters on active medication will experience withdrawal symptoms after their medication is tapered down or discontinued. Note the active successes. Withdrawal symptoms are higher after all subjects were required to begin tapering drug at day 90 (8 of the active quitters reported withdrawal symptoms between day 90 and day 180), and after day 180, the mandatory quit day (7 of the active quitters reported withdrawal Symptoms after day 180).

Local Effects

Mouth /Throat and Cough Subjects were asked about the occurrence of adverse events with open ended questions followed by a mild, moderate or severe rating of the adverse event. There was a very high incidence of local effects (Irritation in Mouth and Throat and Cough) in the active group. By day 14 the difference was no longer present, suggesting that the effect was transient and/or that these subjects dropped out (see dropout table following). Note that the severity in both groups is mild.

Irritation in Mouth and Throat

Day	2	7	14	21
Active				
(N at this visit)	100	81	75	75
# reporting IRR.	31	18	8	3
% of N	31	22	11	4
Mean/Severity	1.2	1.1	1	1
Placebo				
(N at visit)	93	71	51	50
# reporting IRR.	9	6	6	2
n %	10	8	12	4
Mean/Severity	1	1.3	1	-
P-value	.0005	.020	-	-

-The N at visit and p values are from Table 15 of the final study report.
-All subjects did not report the severity.
-P-value is based on Pearson chi-square test
-Severity had 3 categories: 1-mild, 2-moderate, 3-Severe.

Coughing

Day	2	7	14	21
Active (N at visit)	100	81	75	75
# reporting cough	22	13	8	5
% of N	22	16	11	7
Mean/Severity	1.1	1	1	1
Placebo (N at visit)	93	71	51	50
# reporting cough	10	6	3	6
% of N	11	8	6	12
Mean/Severity	1	1.2	1	1
P-value	.036	-	-	-

-The N at visit and p values are from Table 15 of the final study report.
-All subjects did not report the severity.
-P-value is based on Pearson chi-square test
-Severity had 3 categories: 1-mild, 2-moderate, 3-Severe.

Success, Failure and Dropout

Dropouts: Subjects who did not return for a visit for reasons other than starting smoking were classified as dropouts. In the following table, success + failure + dropout = N (112 active, 111 placebo). The dropout rate is slightly higher in the active group at day 2, perhaps related to the local irritant effect of the product as mentioned above. There was no significant difference in dropouts between the two groups at any visit and the total number of dropouts was higher in the control group as expected.

Success, Failure and Dropout

Day	2	7	14.	21	42	90	180
Active (N=112)							
Successes	-	-	-	61	49	36	24
Failures	-	-	-	31	43	53	62
Dropout	13	16	18	20	20	23	26
% dropouts	11.6	14.3	16.1	17.9	17.9	20.5	23.2
Placebo(N-111)							
Successes	-	-	-	37	26	17	12
Failures	-	-	-	47	55	62	64
Dropout	8	15	17	27	30	32	35
% dropouts	7.2	13.5	15.3	24.3	27	28.8	31.5

This is the sponsors classification, values are from the sponsor's summary.

Successes = Known to have been abstinent since the week 2 visit through the indicated week visit

Failures = Known not to have been abstinent since the week 2 visit through the indicated week visit.

Dropouts = The remainder.

Reasons for Dropout

The reasons for dropout as given by the sponsor are listed below. The moderately higher number of dropouts for adverse events in the first weeks on active are probably related to the irritant effect of the inhaler and cough. No unexpected dropout pattern is apparent.

Reasons for Dropout

Day	BL	2	7	14	21	42	90	180	365
Active (N=112)									
Dropout	2	13	16	18	20	20	23	26	32
Reason:									
Non-compliance	0	0	0	1	2	2	2	2	4
Adverse experience	0	8	9	9	9	9	9	9	10
Lost to follow-up	1	1	1	2	3	3	5	8	9
Did not like med	1	3	4	4	4	4	4	4	4
Illness or accident	0	0	0	0	0	0	0	0	2
Other reasons	0	1	2	2	2	2	3	3	3
Placebo(N=111)									
Dropout	1	8	15	17	27	30	32	35	35
Reason:									
Non-compliance	0	2	4	4	6	7	7	8	8
Adverse experience	0	4	6	7	11	11	11	12	12
Lost to follow-up	0	0	1	1	2	4	6	6	6
Did not like meds.	1	2	3	3	5	5	5	5	5
Illness or accident	0	0	1	1	1	1	1	2	2
Other reasons	0	0	0	1	2	2	2	2	2

Table from the sponsor's summary report

Withdrawn due to adverse events

Twenty-two subjects on active drug and 20 subjects on placebo were withdrawn due to adverse events. Nearly all of these were early in the study. Mouth and throat symptoms were mentioned more frequently in the active group (59 Vs 25 %).

Subjects Withdrawn from Study due to Adverse Events

Active

Subject No.	Week/Day	Adverse Event (AE)
	day 2	Sore around mouth, burning sensation
	day 2	Sore throat
	day 2	Foul taste of inhaler, stressful.
	26	Sweating
	52	Sore throat, coughing
	day 2	Dizziness, diarrhoea
	day 2	Irritation of tongue
	day 2	High blood pressure
	day 2	Sore throat, chest tightness, upset stomach
	day 2	Too strong, throat irritation, coughing
	day 2	Dislike taste, throat & mouth irritation, coughing
	day 2	Lips break out, bothers mouth
	12	Possibly AIDS symptoms in mouth
	day 2	Sore throat
	52	Depression (craving)
	1	Sore throat from flu, depression, violence
	day 2	Numbness in throat
	1	Irritation in throat
	day 2	Nervousness (craving)
	52	Terminal lung cancer
	52	Chronic fatigue syndrome
	day 2	Too drowsy to work

Table from the sponsor's summary

Placebo Withdrawals due to Adverse Events

Subjects Withdrawn from Study due to Adverse Events Placebo		
Subject No. Placebo	**Week/day**	**Adverse Events (AE)**
	3	Depressed, anxious
	1	Soreness of tongue & lips
	day 2	Allergic reaction
	day 2	Nausea
	1	Terminal illness
	1	Flu, gagging
	26	Stomach illness, sinus congestion
	day 2	Nausea (due to Menthol)
	3	Hungry, thirsty
	3	Flu, coughing, throat irritation, bronchitis
	1	Wheezing
	3	Sore throat
	day 1	Irritable, violent
	3	Flu
	2	Depressed, anxious (craving)
	3	Mouth raw
	26	Marital stress, soreness in upper mouth plate
	day 2	Nausea, (gagging, vomiting)
	day 2	Difficulty staying awake, diff. conc., abd. pain
	8	Hayfever, hoarseness

Table from the sponsor's summary

Discontinuations

Both the temporary (7 active-8 placebo) and permanent (8 active-7 placebo) discontinuations by the subjects were remarkably similar. A higher drop-out due to higher incidence of mouth and throat symptoms with active is not apparent; most patients rated the mouth and throat symptoms as mild. As in the withdrawal table, taste is mentioned in the active but not in the placebo group.

Temporary Discontinuation of Treatment due to Adverse Events

Subject No. Active	Week/Day	Event
	2	Cold
	3	Cold
	6	Gastritis
	1	Nauseous
	3	Hiccups, pain in ribs
	6	Cold, sore throat
	12	Flu
Subject No. Placebo	**Week/Day**	**Event**
	3	Cold
	2	Bronchitis
	2	Indigestion, heartburn
	2	Sore cheeks, lips sore, lips swollen
	6	Personal stress
	2	Sore throat
	2	Flu
	2	Throat irritated and red

Table from the sponsor's summary

Permanent Discontinuation of Treatment due to Adverse Events

Subject No. Active	Week/day	Event
	day 2	Nausea, light-headedness
	26	Cold
	26	Coughing
	6	Stress, death in family
	6	Sad, stressed over friend's death
	1	Stress
	12	Does not like the taste
	12	Heartburn
Subject No. Placebo	**Week/day**	**Event**
	1	Sore tongue, headache
	6	Stomach problems
	1	Plugged ear, sore throat, congestion, coughing
	3	Flu
	12	Soreness in upper plate of mouth, marital stress
	2	Laryngitis, Hayfever
	day 2	Stress due to back injury

Table from the sponsor's summary

SAFETY SUMMARY

Serious adverse events were reported in both groups but none were considered related to the study drug.

There was a higher incidence of local effects (Irritation in Mouth and Throat and Cough) in the active group at the beginning of therapy. The severity was mild and by day 14 the difference was no longer present.

DISCUSSION

The efficacy is in this study is far better than the efficacy of the first studies of this product. The possible reason is the higher dose; subjects were required to use greater than 4 inhalers per day.

Serious adverse events were reported in this trial, but they are unlikely to be related to the nicotine inhaler. This probably represents a high proportion of serious medical conditions (AIDS, surgery, cancer) in this population.

CONCLUSION:

The Nicotine Inhaler treatment showed substantial efficacy as compared to placebo in this trial.

Throat and mouth irritation and cough were novel effects of this dosage form. No severe or unexpected adverse effects of this therapy were identified.

AW Longmire MD
Medical Review Officer

ED Kramer MD
Peer Review

11-6-96

NDA 20-714

cc:
Orig. NDA 20-714
Div. File
HFD-170/Kramer/Chang Li/Ross/Doddapaneni/Geyer/Permutt/McNeal
HFD-344

NOV 6 1996

McNeal

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

MEDICAL OFFICER REVIEW

NDA: 20-714
SPONSOR: PHARMACIA INC
DRUG: NICOTROL INHALER
TYPE OF SUBMISSION: NEW NDA
PROPOSED INDICATION: SMOKING CESSATION
MEDICAL OFFICER: CHANG QING LI, MD, MSHA, DRPH
PEER MEDICAL OFFICER: E DOUGLAS KRAMER, MD
LETTER DATE BY SPONSOR: 5/01/95
DATE RECEIVED BY CDER:
DATE RECEIVED BY REVIEWER: 5/10/96
DATE REVIEW COMPLETED: 10/31/96
REGULATORY ACTION: APPROVAL
CSO: B McNeal

Integrated Summary of Safety

Summary

The adverse experience profile of Nicotrol Inhaler is similar to that of other currently marketed products of nicotine. Spontaneous adverse events were primarily of 5 types: local events related to the irritant effects of the drug and the dosage form, possible nicotinic effects, events consistent with withdrawal or drug dependence, events likely to be related to the long term effects of smoking, and events of unknown significance, probably unrelated to drug use. The most frequent adverse events are coughing, throat irritation, stomatitis, headache, rhinitis and pharyngitis. Drug abuse and dependence potential among subjects on the active treatment is low. A potential risk associated with the inhaler is the possibility of bronchospasm because of the local irritation effects. The Nicotrol Inhaler is of acceptable risk when administered on ad lib. 4 - 20 inhalers per day.

Background

Nicotine replacement as an aid in smoking cessation is a well accepted treatment. An alternative buccal route of nicotine delivery systems is the nicotine inhaler. The Nicotrol Inhaler has been developed by Pharmacia Inc. The inhaler consists of a mouthpiece and a plastic cartridge containing a porous plug impregnated with nicotine and menthol.

Nicotine is released when air is inhaled through the inhaler. Each inhaler contains about 10 mg of nicotine and 1, mg of l-menthol. Forced inhalation (80 deep inhalations over 20 minutes) releases on the average 4 mg of the nicotine content of each cartridge. About half of the released nicotine is absorbed. Most of the nicotine released from the inhaler adheres to the buccal mucosa. Only a fraction of the dose released, less than 4%, reaches the lower respiratory tract.

Absorption of nicotine through the buccal mucosa is relatively slow. After use of the single inhaler the arterial nicotine concentrations rise to an average of 5 ng/ml in contrast to those of a cigarette, which

reach an average peak of approximately 55 ng/ml within 5 minutes. Ad libitum use of the inhaler typically produces nicotine plasma levels of 6-8 ng/ml, corresponding to about 1/3 of those achieved with cigarette smoking.

The inhaler has been tested in clinical studies against placebo. A total of 1,439 subjects have participated in a total of 6 double-blind randomized placebo-controlled trials conducted in the United States, Denmark and Sweden. Of these individuals, 730 received active treatment with the nicotine inhaler. Another 425 subjects have been exposed to the Nicotine Inhaler from 1 day to 6 months in other clinical trials.

The objective of this review is to evaluate the safety profile of the inhaler in the completed studies. Safety information from the open-label PK studies are also included in some sections.

OVERALL EXTENT OF EXPOSURE

The table below outlines the scope of the entire controlled clinical program. As can be seen, 1,439 subjects have been enrolled in the six studies. Of these, 730 received active treatment with the nicotine inhaler. The inhalers were recommended for ad libitum use within a specified range. For the first three studies, the range was 2 to 10 inhalers per day and for the later three studies the range for two of the studies was 4 to 20 inhalers per day and in study #4 from 4 inhalers per day and up. The recommended duration of inhaler use was 3 months from the start of treatment. The protocols made provisions for inhaler use to continue beyond 3 months for those subjects who felt they were likely to relapse without the inhaler. In these cases, inhaler use could be continued up to 6 months. In most controlled studies, subjects were followed up at 12 months.

Double-blind Randomized Placebo-controlled Independent Studies

Study	Investigators	Dosage Regimen	Follow-up	Study Subjects	Subjects by Treatme
Study #1	Sachs, USA T9ONI01	Ad lib. 2 - 10 inhalers/day	18 months	N = 223	Active = 112 Placebo= 111
Study #2	Glover, USA T9ONI02	Ad lib. 2 - 10 inhalers/day	12 m	N= 241	Active = 129 Placebo= 112
Study #3	T0nnesen, Denmark T90NI03	Ad lib. 2 - 10 inhalers/day	12 m	N= 283	Active = 143 Placebo= 140
Study #4	Hjalmarson, Sweden T91NI04	At least 4 inhalers/day	12 m	N= 247	Active = 123 Placebo= 124
Study #5	Leischow, USA 92NNIN002	Ad lib. 4 - 20 inhalers/day	12 m	N= 222	Active = 111 Placebo= 111
Study #6	Schneider, USA 92NNIN003	Ad lib. 4 - 20 inhalers/day	12 m	N= 223	Active = 112 Placebo= 111
Total				N= 1439	Active = 730 Placebo= 709

daily basis in the controlled studies.

Table. Number of Subjects Using the Nicotine Inhaler Daily

		1 Day		1 Week		3 Weeks		6 Weeks		3 Months		6 Months		> 6 Month
	Total	N	%	N	%	N	%	N	%	N	%	N	%	N
T9ONI01	112	72	64	93	83	74	66	45	40	20	18	7	6	0
T9ONI02	129	117	91	109	84	104	81	80	62	49	38	21	16	0
T9ONI03	143	136	95	119	83	92	64	68	48	41	29	9	6	0
T9INI04	123	105	85	101	82	96	78	69	56	40	33	20	16	0
92NNIN002	111	101	91	96	86	80	72	64	58	45	41	12	11	0
92NNIN003	112	75	67	78	70	72	64	62	55	48	43	12	11	0
Total	730	606	83	596	82	518	71	388	53	243	33	81	11	0

* Data is extracted from the sponsor's reports.

Another 425 subjects have been exposed to the Nicotine Inhaler from 1 day to 6 months in the other clinical trials. These studies are shown in the Table below.

Exposure to the Nicotine Inhaler in other studies

Study	Duration	No. of subjects
Leischow (pilot) (92NNIN002 P)	6 m	30
Schneider (pilot) (92NNIN003 P)	6 m	27
Hjalmarson (pilot) (T9INI04 P)	6 m	32
Nemeth Coslett (Published)	5 d	7
Fagerstrom (21498F)	6 d	83
Hajek (Published)	1 d	20
Nilsson (NIN87 001)	3 w	84
Nilsson (T88NI01)	6 d	25
Nilsson (T88NI02)	1 d	19
Lunell (92NNIN005)	2 d	14
Lunell (T9INI05)	1 d	18
Lunell (T9INI06)	3 d	18
Lunell (92NNIN004)	4 d	5
Lunell (95NNIN011)	5 d	33

* Data is extracted from the sponsor's reports.

Baseline Demographic Characteristics

The table below displays the integrated baseline demographic characteristics by treatment group for the six controlled clinical studies. The study population for these six controlled studies included subjects age 18 years onward.

Table. Baseline Demographic Characteristics by Study and Treatment Group for Each Controlled Study.

Characteristic	T9ONIO1		T9ONI02		T9ONI03		T91NI04		92NNIN002		92NNIN003	
	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
N	112	111	129	112	143	140	123	124	111	111	112	111
Ages												
18 - 25	3	1	0	2	13	19	0	1	3	7	4	0
26 - 40	39	37	61	53	69	63	32	32	45	40	41	41
41 - 60	60	61	65	50	55	44	71	80	51	54	57	59
> 60	10	12	3	7	6	14	20	11	12	10	10	11
Sex												
M	50	51	53	50	60	51	47	42	52	47	72	69
F	62	60	76	62	83	89	76	82	59	64	40	42
Race												
W	101	102	129	111	N/A	N/A	123	124	105	101	100	86
B	4	3	0	1	N/A	N/A	0	0	1	0	8	12
O	7	6	0	0	N/A	N/A	0	0	5	10	4	13
Mean cigs/day	27	27	28	30	20	20	22	21	26	26	29	26
Mean years Smoking Duration	26	28	23	24	21	20	30	29	26	26	25	26

* Data is extracted from the sponsor's reports.

ADVERSE EVENTS IN CLINICAL TRIALS

The ADE data from the six controlled studies were evaluated. Adverse events were collected through questionnaires and through spontaneously reports. Questionnaires focused on withdrawal symptoms and local irritation effects of the inhaler. Inspection of the data set revealed that response to directed questioning was unable to distinguish between active and placebo medication in a way that would be meaningful to physicians and patients using this product (everyone complained about everything). Therefore, the following analyses were based on spontaneously reported events. Spontaneous adverse events were primarily of 5 types: local events related to the irritant effects of the drug and the dosage form, possible nicotinic effects, events consistent with withdrawal or drug dependence, events likely to be related to the long term effects of smoking, and events of unknown significance, probably unrelated to drug use. In order to avoid counting patients more than once, one-event per person was used in this analyses.

Safety analyses in the controlled studies included all subjects who were randomized and received treatment, including quitters, smokers, subjects lost to follow-up or those who did not complete the study period due to ADEs. *Total* adverse events by body system are summarized by treatment outcome (smoker and quitter) in the table below.

The inhaler treatment is associated with increased rates of adverse events especially in Gastro-Intestinal System, Respiratory System and Central and Peripheral Nervous System. The body systems with the most frequently reported ADEs by decreasing frequency were Gastro-Intestinal System, Respiratory System, Central and Peripheral Nervous System and Psychiatric Disorders for both active and placebo. The quitters in both active and placebo reported more AE than the smokers, which may reflect nicotine withdrawal. The average adverse events *per subject* were 2.3 (1262/543), 3.2, 3.3, 4.1 for placebo smokers, placebo quitters, active smokers, and active quitters, respectively.

Adverse Events by Body System in the Controlled Clinical Trials

	Placebo	Placebo	Active	Active
Number Of Patients Treated (A)	543	166	482	248
	Smoker	Quitter	Smoker	Quitter
Total No. ADEs (B)	1,262	534	1593	1024
Average ADE per Subject (B)/(A)	2.3	3.2	3.3	4.1
	N	N	N	N
	Plc-Smk	Plc-Qt	Act-Smk	Act-Qt
GASTRO INTESTINAL SYSTEM DISORD. TOTAL	277	139	453	290
RESPIRATORY SYSTEM DISORDERS TOTAL	235	101	373	229
CENTR & PERIPHERY NERV. SYST. DISORD. TOTAL	178	57	216	101
PSYCHIATRIC DISORDERS TOTAL	152	55	152	94
BODY AS A WHOLE GENERAL DISORDERS TOTAL	105	45	95	80
MUSCULO-SKELETALSYSTEM DISORDERS TOTAL	85	27	77	59
SKIN AND APPENDAGES DISORDERS TOTAL	39	16	39	28
BODY SYSTEM UNKNOWN TOTAL	41	14	32	23
SPECIAL SENSES OTHER, DISORDERS TOTAL	40	13	32	22
ENDOCRINE DISORDERS TOTAL	19	13	20	14
REPRODUCTIVE DISORDERS, FEMALE TOTAL	14	10	26	13
RESISTANCE MECHANISM DISORDERS TOTAL	15	9	14	12
PLATELET, BLEEDIG & CLOTTING DISORDERS	2	4	9	10
URINARY SYSTEM DISORDERS TOTAL	3	2	5	9
VISION DISORDERS TOTAL	14	6	10	7
CARDIOVASCULAR DISORDERS, GENERAL TOTAL	3	7	4	7
HEART RATE AND RHYTHM DISORDERS TOTAL	17	13	14	14
VASCULAR (EXTRACARDIAC) DISORDERS TOTAL	1	1	3	3
AUTONOMIC NERVOUS SYSTEM DISORD. TOTAL	2	1	0	2
HEARING AND VESTIBULAR DISORDERS	8	5	7	2
WHITE CELL AND RED CELL DISORDERS TOTAL	2	1	3	2
LIVER AND BILIARY SYSTEM DISORD. TOTAL	1	0	0	1
MYO , ENDO , PERICARDIAL & VALVE DISORD	0	1	0	0
RED BLOOD CELL DISORDERS TOTAL	0	1	1	0
FETAL DISORDERS TOTAL	0	0	1	0
NEOPLASM TOTAL	1	0	1	0
APPLICATION SITE DISORDERS TOTAL	1	0	0	0
SECONDARY TERMS TOTAL	3	0	2	0

* Data is derived from the sponsor's electronic data sets based on the sponsor's classification. For each subject, a given AE is counted once, but a subject may have more than one event per body system. GI disorders include local irritation effect for the mouth and throat.

The inhaler treatment is strongly associated with local ADEs and possible withdrawal signs or symptoms such as coughing, throat irritation, rhinitis, pharyngitis, stomatitis and pains.

The small amount of nicotine released from the inhaler reaches the lower respiratory tract. A potential risk associated with the inhaler is the possibility of bronchospasm because of the local irritation effects. The magnitude of this risk is unknown because persons with the risk for bronchospasm have not been specifically studied. Nicotine nasal spray, another nicotine product produced by the sponsor, may be capable of excerbating bronchospasm in susceptible individuals. A precautionary language for the risk is included in the labelingof that product.

The most frequently reported systemic ADE was headache except for the quitters in the active treatment. The smokers with the active treatment (Act-Smk) seems to experience more headache (28% vs 20%), and anxiety (16% vs 12%) when compared to the smokers in placebo (Plc-Smk). The increased rates of headache, anxiety and nausea were not observed in the quitters between placebo and the nitotine treatment.

Most Frequent (≥ 4-5%) Adverse Events (*one event/patient*) by Treatment Outcomes in the Controlled Clinical Trials

	Placebo				Active			
Number Of Patients Treated	543		166		482		248	
	Plc-Smk	Plc-Smk	Plc-Qt	Plc-Qt	Act-Smk	Act-Smk	Act-Qt	Act-Qt
COUGHING	52	10%	10	6%	125	26%	74	30%
THROAT IRRITATION	38	7%	13	8%	111	23%	67	27%
STOMATITIS	45	8%	22	13%	81	17%	57	23%
RHINITIS	74	14%	21	13%	83	17%	54	22%
HEADACHE	109	20%	34	20%	137	28%	53	21%
PHARYNGITIS	36	7%	23	14%	67	14%	44	18%
DYSPEPSIA	35	6%	22	13%	56	12%	44	18%
PAIN	28	5%	17	10%	23	5%	28	11%
MOUTH DRY	28	5%	17	10%	27	6%	28	11%
ANXIETY	64	12%	18	11%	76	16%	24	10%
SINUSITIS	27	5%	23	14%	36	7%	22	9%
TASTE COMMENTS	39	7%	8	5%	29	6%	21	8%
INFLUENZA-LIKE SYMPTOMS	23	4%	8	5%	21	4%	20	8%
NAUSEA	34	6%	13	8%	54	11%	19	8%
DIZZINESS	36	7%	12	7%	30	6%	19	8%
SKELETAL PAIN	19	3%	5	3%	16	3%	17	7%
BACK PAIN	34	6%	8	5%	27	6%	16	6%
CHEST PAIN (TIGHTNESS)	14	3%	7	4%	20	4%	15	6%
TOOTH DISORDER	19	3%	11	7%	17	4%	12	5%
PARAESTHESIA	3	1%	3	2%	21	4%	12	5%
MYALGIA	12	2%	6	4%	11	2%	12	5%
FLATULENCE	10	2%	7	4%	20	4%	11	4%
DEPRESSION	11	2%	4	2%	12	2%	11	4%
DIARRHEA	13	2%	6	4%	21	4%	10	4%
INSOMNIA	7	1%	8	5%	12	2%	9	4%
CONSTIPATION	16	3%	6	4%	13	3%	9	4%

* Data is derived from the sponsor's electronic data sets.

The self-reported severity of the four most frequently ADE (coughing, throat irritation, stomatitis and headache) were examined. In general, the severity of ADEs was not correlated with the inhaler treatment.

The possible cardiovascular efffects of nicotine such as tachycardia were seen in subjects on the inhaler. The increased rate of palpatation in the active treatment is small, but may be real. Hypertension is evenly distributed in the active treatment and placebo, and reflects baseline condition. The overall cardiovascular efffects among subjects on active treatment is small, and is similar to other products in this class.

Cardiovascular Adverse Events (*one event/patient* by Treatment Outcomes in the Controlled Clinical Trials

	Placebo		Active	
Number Of Patients Treated	543	166	482	248
	Plc-Smk	Plc-Qt	Act-Smk	Act-Qt
HYPERTENSION	2	7	3	5
PALPITATION	2	0	4	3
TACHYCARDIA	1	0	0	3
VASCULAR DISORDER	1	0	2	1
CEREBROVASCULAR DISORDER	0	0	1	0
HYPOTENSION	1	0	0	0
ANGINA PECTORIS	0	1	0	0
ARRHYTHMIA	0	0	1	0

* Data is derived from the sponsor's electronic data sets.

Adverse Events in Demographic Subgroups

The incidence of adverse experiences in the controlled clinical trials was examined for each treatment group, stratified by age categories (20-39 yr, 40-49 yr, 50-59 yr, and ≥ 60 yr) and gender. Race was not used as a stratification variable because the study population was predominantly Caucasian. No apparent relationship with patient age was observed for the overall incidence of adverse events. For individual events, slightly higher incidences of stomatitis, back pain, influenza-like symptoms, dizziness and taste comments were observed in patients 60 years or older than in the younger age categories.

Trials

	Age Groups				%			
AE	20 - 39 yrs	40 - 49 yrs	50 - 59 yrs	> 60 yrs	21 - 39 yrs	41 - 49 yrs	51 - 59 yrs	> 60 yrs
HEADACHE	123	119	67	22	22%	25%	25%	17%
RHINITIS	95	77	39	20	17%	16%	14%	15%
COUGHING	79	94	62	24	14%	20%	23%	18%
STOMATITIS	75	73	33	23	13%	15%	12%	17%
DYSPEPSIA	72	51	20	14	13%	11%	7%	11%
THROAT IRRITATION	68	82	55	23	12%	17%	20%	17%
PHARYNGITIS	64	52	42	12	11%	11%	16%	9%
ANXIETY	54	67	45	14	9%	14%	17%	11%
NAUSEA	45	32	32	11	8%	7%	12%	8%
PAIN	44	28	14	9	8%	6%	5%	7%
SINUSITIS	43	36	20	8	8%	8%	7%	6%
MOUTH DRY	36	34	19	11	6%	7%	7%	8%
BACK PAIN	33	25	15	12	6%	5%	6%	9%
TOOTH DISORDER	32	14	12	1	6%	3%	4%	1%
INFLUENZA-LIKE SYMPTOMS	26	24	12	10	5%	5%	4%	8%
DIZZINESS	25	27	32	12	4%	6%	12%	9%
CHEST PAIN (TIGHTNESS)	25	9	17	4	4%	2%	6%	3%
TASTE COMMENTS	24	29	23	20	4%	6%	9%	15%
FLATULENCE	24	15	7	2	4%	3%	3%	2%
SKELETAL PAIN	23	14	15	5	4%	3%	6%	4%
MYALGIA	20	16	2	3	4%	3%	1%	2%
DIARRHEA	19	20	6	5	3%	4%	2%	4%
EDEMA	18	8	6	6	3%	2%	2%	5%
ARTHRALGIA	18	5	5	3	3%	1%	2%	2%
CONSTIPATION	17	18	5	4	3%	4%	2%	3%
INSOMNIA	17	11	4	4	3%	2%	1%	3%
WITHDRAWAL	16	6	5	3	3%	1%	2%	2%
	570	472	270	132				

* Data is derived from the sponsor's electronic data sets.

When stratified by sex, females generally had slightly more adverse events than males. The pattern or order of frequencies of adverse events, however, is similar between gender.

Most Frequent (≥3%) Adverse Events (*one event/patient*) by Gender in the Controlled Clinical Trials

	FEMALE (N)	%	MALE (N)	%
HEADACHE	194	24%	137	21%
COUGHING	166	21%	93	14%
THROAT IRRITATION	141	18%	87	14%
RHINITIS	139	17%	92	14%
STOMATITIS	132	17%	72	11%
PHARYNGITIS	109	14%	61	9%
DYSPEPSIA	86	11%	71	11%
NAUSEA	79	10%	41	6%
TASTE COMMENTS	68	9%	28	4%
MOUTH DRY	59	7%	41	6%
DIZZINESS	55	7%	41	6%
INFLUENZA-LIKE SYMPTOMS	44	6%	28	4%
PARAESTHESIA	23	3%	16	2%
NERVOUSNESS	21	3%	8	1%
Total	798		644	

* Data is derived from the sponsor's electronic data sets.

The incidence of adverse experiences by gender was further examined for each clinical trials in the table below. Considerable variations in adverse events were observed when compared the US study sites and the European sites. For example, the two European studies (study #3 and #4) reported much lower frequencies in headache, rhinitis and pharyngitis. The unique adverse events were 613 (stduy #3) and 459 (study #4) in the European studies as compared to 794 (study #1), 943 (study #2), 816 (study #5) and 922 (study #6) in the US studies.

Most Frequent Adverse Events (*one event/patient*) by Gender and Clinical Trials

	Study #1		Study #2		Study #3		Study #4		Study #5		Study #6	
AE	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
HEADACHE	61	44	71	47	9	9	1	0	32	27	20	10
RHINITIS	32	26	40	32	2	1	8	3	30	16	27	14
COUGHING	17	5	17	6	44	29	31	12	24	20	33	21
PHARYNGITIS	14	9	11	8	9	4	15	11	30	13	30	16
DYSPEPSIA	14	12	21	16	9	8	9	9	19	13	14	13
STOMATITIS	6	3	11	7	26	23	15	6	35	18	39	15
THROAT IRRITATION	4	2	4	2	45	36	27	15	24	18	37	14
DIZZINESS	4	2	12	10	10	10	0	0	11	8	18	11
MOUTH DRY	4	5	1	4	15	6	13	8	11	8	15	10
NAUSEA	3	5	12	7	18	9	15	6	12	6	19	8
NERVOUSNESS	3	1	4	1	1	1	0	0	1	5	12	0
PARAESTHESIA	3	2	1	2	0	1	2	4	5	5	12	2
TASTE COMMENTS	2	1	2	2	10	3	9	5	12	6	33	11
INFLUENZA-LIKE SYMPTOMS	2	3	8	12	2	0	0	0	7	4	25	9
TOTAL AE (INCLUDED AE NOT LISTED HERE)	476	318	541	402	367	246	293	166	500	316	628	294
TOTAL SUBJECTS	122	101	139	103	174	111	158	89	123	99	82	141
HEADACHE	50%	44%	51%	46%	5%	8%	1%	0%	26%	27%	24%	7%
RHINITIS	26%	26%	29%	31%	1%	1%	5%	3%	24%	16%	33%	10%
COUGHING	14%	5%	12%	6%	25%	26%	20%	13%	20%	20%	40%	15%
PHARYNGITIS	11%	9%	8%	8%	5%	4%	9%	12%	24%	13%	37%	11%
DYSPEPSIA	11%	12%	15%	16%	5%	7%	6%	10%	15%	13%	17%	9%
STOMATITIS	5%	3%	8%	7%	15%	21%	9%	7%	28%	18%	48%	11%
THROAT IRRITATION	3%	2%	3%	2%	26%	32%	17%	17%	20%	18%	45%	10%
DIZZINESS	3%	2%	9%	10%	6%	9%	0%	0%	9%	8%	22%	8%
MOUTH DRY	3%	5%	1%	4%	9%	5%	8%	9%	9%	8%	18%	7%
NAUSEA	2%	5%	9%	7%	10%	8%	9%	7%	10%	6%	23%	6%
NERVOUSNESS	2%	1%	3%	1%	1%	1%	0%	0%	1%	5%	15%	0%
PARAESTHESIA	2%	2%	1%	2%	0%	1%	1%	4%	4%	5%	15%	1%
TASTE COMMENTS	2%	1%	1%	2%	6%	3%	6%	6%	10%	6%	40%	8%
INFLUENZA-LIKE SYMPTOMS	2%	3%	6%	12%	1%	0%	0%	0%	6%	4%	30%	6%

* Data is derived from the sponsor's electronic data sets.

Adverse Events in the Two Pivotal Studies (Study #5 and #6)

The two pivotal studies (#5 and #6) were high dose trials, and in general research subjects reported more adverse events than the low dose trails. Sources of adverse events included both questionnaires and spontaneous reports. Including all sources, nearly 4700 adverse events were recorded in *study #5*, and slightly more than 4300 adverse events were recorded in *study 6*. For subjects on both treatments, about 1/3 of adverse events were spontaneously reported and 2/3 were elicited in response to directed questioning. Spontaneous adverse events were primarily of 5 types: local events related to the irritant effects of the drug and the dosage form (irritation of the throat, mouth or lips, coughing), possible nicotinic effects (dyspepsia, dizziness), events consistent with withdrawal or drug dependence (restlessness, etc.), events likely to be related to the long term effects of smoking (bronchitis etc.), and events of unknown significance, probably unrelated to drug use (headaches, flu etc.). Common spontaneously reported nonserious events (5% or greater incidence) are listed in the following table.

Adverse Events in Study #5

Local irritant effects included irritation to the throat, mouth, tongue or lips. Other local effects included coughing, rhinitis and pain in the jaw or neck.

Dyspepsia was the most prominent of the nicotinic effects, with hiccup notably absent in placebo but reported by 5 subjects on active drug. Palpitations or tachycardia were reported by 1 subject on each treatment.

Withdrawal symptoms were reported by slightly more subjects on active than placebo.

The number of subjects reporting a given adverse event is given in the following tables based on the reviewer's assessment of the type of event.

Possible Local Effects in study #5

Adverse Event	Active	Placebo
IRRITATION LOCAL	73	46
COUGHING	35	9
RHINITIS	33	13
PAIN JAW/NECK	10	6
SINUSITIS	7	9
TASTE COMMENTS	5	13
TOOTH DISORDER	5	6
DYSPHONIA	2	0
PRACTICAL PROBLEMS	2	1
ASTHMA	1	1
BRONCHOSPASM	1	0
CONJUNCTIVITIS	1	2
SALIVA INCREASED	1	2
PAROSMIA	0	1

Table made by the reviewer based on recoding of the sponsor's electronic data set.

Possible Nicotinic Effects in Study #5

Adverse Event	Active	Placebo
DYSPEPSIA	22	10
DIARRHEA	8	3
NAUSEA	6	6
HICCUP	5	0
SWEATING INCREASED	2	0
PALPITATION	1	0
TACHYCARDIA	0	1

Table made by the reviewer based on recoding of the sponsor's electronic data set.

Possible Nicotine Withdrawal in Study #5

Adverse Event	Active	Placebo
ANXIETY	12	8
DIZZINESS	12	8
MYALGIA	7	3
DEPRESSION	5	2
DRUG DEPENDENCE	5	2
FATIGUE	4	1
IRRITABILITY	4	0
SLEEP DISORDER	4	4
CONCENTRATION IMPAIRED	3	5
EMOTIONAL LABILITY	3	0
WITHDRAWAL SYNDROME	3	3
APPETITE INCREASED	2	0
SOMNOLENCE	2	1
AGITATION	1	2
APATHY	1	1
TREMOR	1	0
CONFUSION	0	3

Table made by the reviewer based on recoding of the sponsor's electronic data set.

Possible Smoking Related Disorders in Study #5

Adverse Event	Active	Placebo
CHEST DISCOMFORT	8	4
BRONCHITIS	4	2
DYSPNOEA	2	0
HYPERTENSION	1	0
SPUTUM INCREASED	1	0

Table made by the reviewer based on recoding of the sponsor's electronic data set.

Study Emergent Events in Study #5

Adverse Events	Active	Placebo
HEADACHE	38	22
PAIN	13	11
PAIN BACK	12	2
ALLERGY	11	8
PARAESTHESIA	6	0
INFLUENZA-LIKE SYMPTOMS	5	6
PRURITUS	5	0
CONSTIPATION	4	4
FLATULENCE	4	2
INSUFFICIENT INFO.	4	7
FEVER	3	0
MENSTRUAL DISORDER	3	0
THIRST	3	0
ABDOMINAL PAIN	2	4
ACCIDENT	2	0
ACNE	2	1
BURSITIS	2	0
EDEMA	2	0
FLUSHING	2	2
INFECTION	2	3
MALAISE	2	0
NEPHRITIS INTERSTITIAL	2	0
PAIN MOUTH	2	2
POLYURIA	2	0
URINARY TRACT INFECTION	2	1
ARTHRITIS	1	1
ASTHENIA	1	1
DYSMENORRHOEA	1	0
EAR DISORDER	1	2
EPISTAXIS	1	2
GOUT	1	0
GUM HYPERPLASIA	1	1
HEPATITIS	1	0
HERPES SIMPLEX	1	0
INFECTION VIRAL	1	0
LYMPHADENOPATHY	1	1
MUSCLE WEAKNESS	1	0
EDEMA	1	0
EDEMA GENERALIZED	1	0
PREMENSTRUAL TENSION	1	0
RASH	1	0
RIGORS	1	0
SKIN DISORDER	1	0
UPPER RESP TRACT INFECTION	1	1

Possibly Unrelated Events		
Adverse Events	Active	Placebo
VERTIGO	1	0
WEIGHT DECREASE	1	0
ANOREXIA	0	1
ARTHRALGIA	0	1
CRAMPS LEGS	0	1
CYSTITIS	0	1
GLAUCOMA	0	1
LEG PAIN	0	2
MYDRIASIS	0	1
EDEMA LEGS	0	1
VISION ABNORMAL	0	1

Table made by the reviewer based on recoding of the sponsor's electronic data set.

A total of 7 subjects in this study (5 on active medication, 2 on placebo) reported symptoms of possible drug dependence. The experiences of these subjects are described below.

Subjects reporting possible drug dependence in Study #5

Subject	Event	Outcome	Last Drug Dispensed
placebo 57 yo M, FTQ=8, 35cig/day	ineffective and no satisfaction day 2	Failure	Study Start
placebo 53 yo F, FTQ=7, 20 cig/day	satisfaction level down and craving day 7	Failure	Day 7
active 52 yo F, FTQ=7, 20 cig/day	drug dependence day 180; malaise, fatigue day 14, 21	6 week Success	Day 90
active 66 yo F, FTQ=6, 18 cig/day	increased appetite, difficulty concentrating, headache, craving, drug dependence day 180. No other AE's reported during trial.	6 week Success	Day 90
active 48 yo M, FTQ=10, 60 cig/day	Drug dependence (inhaler) reported at 180 days. No other WD reported.	6 week Success	Day 90
active 40 yo M, FTQ=3, 13 cig/day	Drug dependence (inhaler) reported at day 180. Stress reported days 180, 365. No other WD.	Failure	Day 90
active 25 yo F, FTQ=9, 35 cig/day	Drug dependence (inhaler) reported day 180. Reported crying for no reason day 7	Failure	Day 90

Table made by the reviewer based on recoding of the sponsor's electronic data set.

Among subjects on placebo, reports possibly involving drug dependence occur early in the trial and (correctly) involve the subject's observation that there is no therapeutic benefit from the inhaler. Among subjects on active drug the situation is quite different. Reports of dependence refer to the inhaler itself and they emerge in all cases at the first visit after the last day the drug has been stopped. Interestingly, subjects who report dependence do not seem to have previously reported a lot of withdrawal, nor have they been able to stop smoking.

Number of subjects reporting withdrawal symptoms by treatment group and 6 week outcome

	2	7	14	21	42	90	180	365
Active Fail	9	10	9	7	3	0	3	1
Active Quit	7	4	5	3	3	1	9	6
Placebo Fail	17	15	7	3	1	0	0	0
Placebo Quit	0	0	0	1	1	1	2	2

Table made by the reviewer based on recoding of the sponsor's electronic data set.

Early in this study, placebo quitters had the fewest spontaneously reported withdrawal events during the first weeks of the trial, while failures had the most withdrawal. It is notable that among the active quitters, there is a re-emergence of withdrawal symptoms following day 90 (the last day drug was available for dispensing in this trial).

Adverse Events in Study #6

Number of subjects spontaneously reporting adverse events in study #6

RECODE	Active N=112	Placebo N=111	Grand Total N=223
IRRITATION LOCAL	73	47	120
COUGHING	37	17	54
TASTE COMMENTS	27	18	45
RHINITIS	19	22	41
INFLUENZA-LIKE SYMPTOMS	20	14	34
HEADACHE	19	11	30
DIZZINESS	12	17	29
DYSPEPSIA	18	9	27
NAUSEA	13	11	24
SLEEP DISORDER	11	11	22
ANXIETY	11	7	18
PAIN BACK	6	8	14
TOOTH DISORDER	6	7	13
DIARRHEA	7	5	12
DEPRESSION	7	4	11
WITHDRAWAL SYNDROME	7	4	11
HYPERTENSION	6	3	9
CONSTIPATION	4	5	9
CONCENTRATION IMPAIRED	3	6	9
IRRITABILITY	2	7	9
PAIN JAW/NECK	2	7	9
FATIGUE	7	1	8
PARAESTHESIA	7	1	8
CHEST DISCOMFORT	5	3	8
PRACTICAL PROBLEMS	2	6	8
SINUSITIS	4	3	7
BRONCHITIS	3	4	7
FLATULENCE	3	4	7
APPETITE INCREASED	2	5	7

Table made by the reviewer based on recoding of the sponsor's electronic data set.

Note that while some likely nicotine withdrawal symptoms (e.g. irritability, impaired concentration) seem to be reported somewhat more frequently in placebo subjects others (e.g. anxiety) are reported with equal frequency between groups. Still other possible withdrawal symptoms (e.g. fatigue) are more common among subjects on active medication. The overall number of subjects reporting at least 1 possible withdrawal symptom is approximately the same between treatment groups. This could reflect either a subtle imbalance between treatment groups in their severity of dependence on nicotine at baseline (unlikely) or it could reflect the fact that more dependent smokers were able to quit on active drug (these subjects would be more likely to both experience withdrawal symptoms yet stay in the trial to report them).

A total of 6 subjects (2 on active medication and 4 on placebo) reported symptoms of possible drug dependence in *study #6*. These patients are described below:

Subject	Report	Outcome	Last drug dispensed
placebo, 38,M 30cig/day FTQ=6	Felt addicted to inhaler (day 7)	6 week success 1 year failure	Day 42
placebo, 65 M 20cig/day FTQ=6	Not strong enough (day 2)	6 week success 1 year failure	Day 21
active 36 M 20cig/day FTQ=7	Drinking a lot of alcohol (day 180)	6 week success 1 year failure	Day 90
placebo 63 F 20cig/day FTQ=7	Inhaler not helping (day 2)	6 week failure 1 year failure	Day 21
active 50 M 30cig/day FTQ=9	inhaler too weak (day 2)	6 week success 1 year failure	Day 90
placebo 49 M 20cig/day	Necessary to use inhaler constantly (day 2)	6 week success 1 year success	Day 21

Table made by the reviewer based on recoding of the sponsor's electronic data set.

Five of these reports occurred early in treatment, and 4 of those 5 were reports by subjects on placebo who believed (correctly) that their medication lacked effect. Of the 2 subjects on active drug who reported possible drug dependence, both had drug dispensed to them for the maximum length of time allowed and one of them reported excessive drinking at the visit following the last visit at which inhalers were dispensed. This difference suggested that some patients on active drug may have experienced withdrawal symptoms at the time that tapering of the inhalers began. This is explored in the following table:

Number of Patients reporting possible withdrawal symptoms by study day by 6 week outcome in study #6

Day of Study	0	2	7	14	21	42	90	180	365
Active Failures	0	16	6	4	2	4	2	0	0
Active Successes	1	10	7	4	4	8	3	8	7
Placebo Failures	0	22	6	5	2	2	0	0	0
Placebo Successes	1	7	5	3	4	3	1	0	0

Table made by the reviewer from the sponsor's electronic data set. 49 active and 26 placebo subjects were successfully abstinent at week 6.

This data suggests that successful quitters on active medication will continue to experience withdrawal symptoms during treatment. The data from week 6 on, suggest that some of these patients may experience withdrawal as they begin to taper their inhaler use.

There were a total of nine other clinical studies in a total of 206 subjects. These studies include six Phase I/II studies in which 117 subjects were treated with the Nicotine Inhaler and three Phase III pilot studies (protocol T9INI04, 92NNIN002 and 92NNIN003) in which 89 subjects were treated with the Nicotine Inhaler.

Local reactions including cough and throat irritation were the most frequently reported ADEs in these studies. The most frequently reported systemic ADEs were headache and dizziness.

In the Phase III pilot studies, one death (92NNIN002, Pat. No. and one serious non-fatal ADE (92NNIN003, Pat. No. were reported (see details below).

Deaths, Serious Adverse Experiences and Discontinuations Due to Adverse Experiences

Data on all serious adverse events, adverse experiences that resulted in death or discontinuation, and all potentially serious adverse experiences that did not prevent the patient from continuing in the study are reported in this section.

Death and Serious AE reported under This NDA

		No. of Subjects
Exposure #1	6 Placebo Controlled Clinical Trials	
	Total Subjects	730
	Total Nicotine Inhaler Exposures	730
	Serious Reports (Excluding deaths)	10
	Deaths	1
Exposure #2	Other Clinical Trials	
	Total Subjects	425
	Total Nicotine Inhaler Exposures	425
	Serious Reports (Excluding deaths)	1
	Deaths	1
	TOTALS	
	Total Nicotine Inhaler Exposures	1155
	Serious Reports (Excluding deaths)	11
	Deaths	2

* Data is extracted from the sponsor's reports.

Deaths

A total of two deaths occurred in patients participating in the clinical studies reported in this Integrated Summary of Safety. None of the reported deaths was attributable to study medication, but rather to diseases clearly associated with smoking.

One subject in the controlled study T9ONI02, was withdrawn from the study due to a serious ADE and later died. The subject (No. was a 43 years old male (smoking for 20 years, 25 cigarettes per day) with heart murmur, who after cardiology examination was found to have a defective heart valve and a 6.5 cm aneurysm. Upon decision for an open heart surgery the subject was removed from the study at the 3 months visit, on May 10, 1991. The subject had occasional slips. During the 3 months study period the

subject used 180 *active inhalers* and smoked 160 cigarettes the first 6 weeks and another 20 cigarettes one week before the 3 months visit. On May 18. 1991. following complications during surgery, the subject died.

One subject in pilot study 92NNIN002 (No.) who was a 67 year old male (smoking for 48 years. 50 non-filter cigarettes per day) died from left brain hemorrhage. The subject entered the study on July 14, 1992. At the 6 week visit the subject used an average of 4 *nicotine inhalers* per day and stopped using the inhaler at this visit. The subject returned for his 3 month visit on October 21, 1992. From the quit day the subject has been completely abstinent. The subject never returned for his next visit at 6 months. The subject was admitted to hospital on November 8, 1992 and died on November 12, 1992.

Serious Clinical Adverse Drug Experiences (Excluding Deaths) for All Clinical Studies

In these six studies, 9 subjects reported 10 nonfatal serious ADEs giving an incidence of total serious ADEs of 1.40% (n = 730). One subject had one serious AE in other clinical studies (425 Nicotine Inhaler treated subjects). These ADEs were not considered to be drug related. In comparison, 6 subjects reported 9 nonfatal serious ADEs in placebo.

Serious Clinical Adverse Drug Experiences in the Inhaler Treatment

Study No.	pid	Treatment	Diagnosis
T9ONI01		Active	Cancer of left lung
		Active	Depression
T9ONI02		Active	Defective heart valve, aneurysm
T9ONI03		Active	Migraine and transient cerebral
92NNIN002		Active	Chest pain
92NNIN003		Active	Shoulder surgery
		Active	Foot surgery left toe and right toe
		Active	Foot surgery right toe
		Active	Purple lesions on face, flu, Possible Kaposi's sarcoma and AIDS
		Active	Terminal Lung Cancer
92NNIN003 (pilot)		Active	Prostate surgery

* Data is extracted from the sponsor's reports.

A total of 44 (6%) subjects on Nicotine Inhaler treatment withdrew from the clinical trials after randomization out of a total of 730 patients, and 46 subjects on placebo treatment withdrew. The most frequently reported reasons for study withdrawal in the Nicotine Inhaler treated group were sore throat, throat irritating, coughing and headache.

Time of Withdrawal by Treatment

Withdrawal Time	Treatment		
Week	Placebo	Active	Total
1	17	23	40
2	9	1	10
3	10	2	12
6	4	5	9
8	1	0	1
12	0	4	4
26	5	3	8
52	0	6	6
Grand Total	46	44	90

* Data is derived from the sponsor's electronic data sets.

Patients Who Withdrawn from Clinical Studies Due to Adverse Events

Treatment	Study No.	pid	Week	Event
Active	1		1	Recurrent urticaria
Active	1		6	Inhaler caused nasal congestion
Active	1		26	Depression
Active	1		52	Cancer of left lung
Active	2		12	Open heart surgery
Active	2		12	Irritation in throat
Active	4		6	Pain/burn in throat
Active	4		1	Nausea
Active	4		12	Nausea
Active	4		3	Heart failure due to irregular pulse
Active	4		6	Corrosive symptoms in mouth
Active	5		1	Throat irritation, dizzy spells
Active	5		3	Throat irritation, coughing, allergy, hoarse voice,
Active	5		6	Stress, work problems, bronchitis
Active	5		52	Lost job, stress, headache, gas
Active	5		2	Light headache, general weakness, nausea, sore throat,
Active	5		6	Heartburn
Active	5		26	Headache, difficulty concentrating, eating more (craving)
Active	5		1	Headache, coughing
Active	5		1	Excess saliva, diarrhea
Active	5		1	Coughing
Active	5		1	Anxiety, nervousness, paranoia
Active	6		1	Too strong, throat irritation, coughing
Active	6		1	Too drowsy to work
Active	6		52	Terminal lung cancer
Active	6		26	Sweating
Active	6		52	Sore throat, coughing
Active	6		1	Sore throat, chest tightness, upset stomach
Active	6		1	Sore throat
Active	6		1	Sore throat
Active	6		1	Sore around mouth, burning sensation
Active	6		12	Possibly AIDS symptoms in mouth
Active	6		1	Numbness in throat
Active	6		1	Nervousness (craving)
Active	6		1	Lips break out, bothers mouth
Active	6		1	Irritation of tongue
Active	6		1	Irritation in throat
Active	6		1	High blood pressure
Active	6		1	Foul taste of inhaler, stressful circumstances
Active	6		1	Dizziness, diarrhea
Active	6		1	Dislike taste, throat and mouth irritation, coughing
Active	6		52	Depression (craving)
Active	6		52	Chronic fatigue syndrome
Active	6		1	Sore throat from flu, depression, violence

* Data is extracted from the sponsor's reports.

Patients Who Withdrawn from Clinical Studies Due to Adverse Events

Placebo	1	2	Depression
Placebo	1	2	Inhalers gave sore throat
Placebo	2	6	Lump in throat
Placebo	2	26	Started smoking as a result of pain from old injury
Placebo	2	6	Felt depressed
Placebo	4	3	Illness
Placebo	4	26	Ulcer
Placebo	4	1	Blood pressure falling too much
Placebo	5	2	Headache
Placebo	5	3	Headache
Placebo	5	1	Disorientation
Placebo	5	26	Edematous mouth, upper and lower respiratory tract infection
Placebo	5	2	Menthol irritation, sore throat
Placebo	5	2	Reduced concentration ability, irregularity, diarrhea
Placebo	5	2	Weight gain, coughing
Placebo	5	2	Cool numbing sensation at the top of the throat
Placebo	5	6	Dry mouth, bad taste
Placebo	5	1	Tightness in chest, chest pain
Placebo	5	1	Rising blood pressure, anxiety, inability to concentrate
Placebo	5	2	Nausea, ear infection, coughing, cold and flu, menthol irritation
Placebo	5	1	Illness or accident unrelated to the inhaler
Placebo	5	1	General weakness
Placebo	5	3	Constipation, gas, leg cramps, swollen legs, bad taste in mouth
Placebo	5	6	Ulcer on tongue
Placebo	5	1	Scratchy throat
Placebo	5	3	Anxiety, tightness in chest
Placebo	6	3	Depressed, anxious
Placebo	6	1	Soreness of tongue and lips
Placebo	6	1	Allergic reaction
Placebo	6	1	Nausea
Placebo	6	1	Terminal illness
Placebo	6	1	Flu, gagging
Placebo	6	26	Stomach illness, sinus congestion
Placebo	6	1	Nausea (due to menthol)
Placebo	6	3	Hungry, thirsty
Placebo	6	3	Flu, coughing, throat irritation, bronchitis
Placebo	6	1	Wheezing
Placebo	6	3	Sore throat
Placebo	6	1	Irritable, violent
Placebo	6	3	Flu
Placebo	6	2	Depressed, anxious (craving)
Placebo	6	3	Mouth raw
Placebo	6	26	Marital stress, soreness in the upper plate of mouth
Placebo	6	1	Nausea,(gagging, vomiting)
Placebo	6	1	Difficulty staying awake, difficulty concentrating, abdominal pain
Placebo	6	8	Hay fever, hoarseness

* Data is extracted from the sponsor's reports.

Subjects discontinued their medication Due to Adverse Drug Experiences in Controlled Studies

Due to Adverse Drug Experiences a total of 59 subjects (8%) on Nicotine Inhaler treatment and 43 subjects (6%) on placebo treatment permanently discontinued their medication due to an Adverse Drug Experience and/or Stressful Event. Also 61 subjects (8.4%) in the Nicotine Inhaler group and 40 subjects (5.7%) in the placebo group temporarily discontinued their medication due to an Adverse Drug Experience and/or Stressful Event. Out of these 61 subjects, 14 subjects on Nicotine Inhaler and 10 subjects on placebo treatment later also permanently discontinued their medication. The most frequently reported reasons for permanent and/or temporary discontinuation of treatment are sore throat, throat irritation, coughing and stress.

Summary and Conclusions

The adverse experience profile of the Nicotine Inhaler is similar to that of other currently marketed products of nicotine. From the data presented the following conclusions are supportable:

1) The most frequent adverse events are coughing, throat irritation, stomatitis, headache, rhinitis and pharyngitis. A potential risk associated with the inhaler is the possibility of bronchospasm because of the local irritation effects. The magnitude of this risk, however, is unknown because few persons with the risk for bronchospasm have been studied. Further studies in susceptible population should be considered. Nicotine nasal spray, another nicotine product produced by the sponsor, may be capable of exacerbating bronchospasm in susceptible individuals. A precautionary language for the risk is included in the labeling for that product. The labeling for the nicotine inhaler may adopt a similar language.

2) The differences in adverse experiences by age and sex are small.

3) Slightly higher incidences of stomatitis, back pain, influenza-like symptoms, and dizziness were observed in patients 60 years or older than in the younger age categories.

4) Successful quitters on active medication will continue to experience withdrawal symptoms during treatment. Some of these patients may experience withdrawal as they begin to taper their inhaler use.

5) The Nicotine Inhaler is of acceptable risk when administered on ad lib. 4-20 inhalers per day.

6) Withdrawal symptoms were reported by slightly more subjects on active than placebo. Subjects who report dependence do not seem to have previously reported a lot of withdrawal, nor have they been able to stop smoking among the active quitters, there is a re-emergence of withdrawal symptoms following day 90

7) Drug abuse and dependence potential among subjects on the active treatment is acceptable.

CC: Original NDA
HFD-170 Division File
HFD-170 C Li
HFD-170 CSO B McNeal

Chang Qing Li 11/6/96
Chang-Qing Li
Medical Review Officer

E Douglas Kramer 11-6-96
Peer Reviewer
E Douglas Kramer, MD

Appendix

List of the Adverse Events (One Event/Patient) by Body System in the Six Controlled Clinical Trials

Data is derived from the sponsor's electronic data sets based on the sponsor's classification. For each subject, a given AE is counted once, but a subject may have more than one event per body system.

Adverse Events by Body System in the Controlled Clinical Trials

	Plc-Smk	Plc-Qt	Act-Smk	Act-Qt
ACNE	1	2	5	2
ALOPECIA	0	0	1	0
BULLOUS ERUPTION	9	6	13	6
DERMATITIS	0	0	0	1
ECZEMA	0	0	1	0
NAIL DISORDER	1	0	0	0
PRURITUS	5	3	5	3
RASH	6	5	3	6
SEBORRHEA	1	0	0	0
SKIN DISORDER	0	0	1	4
SWEATING INCREASED	8	0	5	3
URTICARIA	8	0	5	3
SKIN AND APPENDAGE DISORDERS TOTAL	39	16	39	28
ARTHRALGIA	9	4	12	6
ARTHRITIS	3	2	3	3
ARTHROPATHY	0	1	1	0
ARTHROSIS	3	0	2	2
BACK PAIN	34	8	27	16
BURSITIS	1	0	3	0
FRACTURE PATHOLOGICAL	0	0	1	0
GOUT	0	1	0	1
MUSCLE WEAKNESS	1	0	1	1
MYALGIA	12	6	11	12
MYOPATHY	1	0	0	1
OSTEOPOROSIS	1	0	0	0
SKELETAL PAIN	19	5	16	17
TENDINIIIS	1	0	0	0
MUSCULO-SKELETAL SYSTEM DISORDERS TOTAL	85	27	77	59
CONVULSIONS	1	0	1	0
CRAMPS LEGS	1	2	2	0
DIZZINESS	36	12	30	19
DYSPHONIA	6	1	4	7
HEADACHE	109	34	137	53
HYPERAESTHESIA	1	0	0	1
HYPERKINESIA	0	0	1	0
HYPERTONIA	1	1	3	0
HYPOAESTHESIA	5	1	2	2
HYPOKINESIA	0	0	1	1
LEG PAIN	3	0	0	1
MIGRAINE	3	1	6	1
NEURALGIA	1	0	0	1
PARAESTHESIA	3	3	21	12
PARALYSIS	0	0	1	0
SENSORY DISTURBANCE	1	0	0	0
TONGUE PARALYSIS	1	1	3	1
TREMOR	3	0	4	0
VERTIGO	3	1	0	2
CENTR & PERIPHER NERV. SYST. DISORD. TOTAL	178	57	216	101
FLUSHING	1	1	0	2
PUPILLARY REFLEX IMPAIRED	1	0	0	0
AUTONOMIC NERVOUS SYSTEM DISORD. TOTAL	2	1	0	2

Adverse Events by Body System in the Controlled Clinical Trials

	Plc-Smk	Plc-Qt	Act-Smk	Act-Qt
CATARACT	0	0	1	0
CONJUNCTIVITIS	6	2	5	6
DIPLOPIA	0	1	0	0
EYE PAIN	1	1	1	0
EYELID RETRACTION	0	0	1	0
GLAUCOMA	1	0	0	0
IRRITATION EYE	0	0	1	0
KERATITIS	1	0	0	0
VISION ABNORMAL	5	2	1	1
VISION DISORDERS TOTAL	14	6	10	7
EAR DISORDER NOS	2	0	0	1
EARACHE	4	4	5	0
HEARING DECREASED	0	1	0	1
TINNITUS	2	0	2	0
HEARING AND VESTIBULAR DISORDERS	8	5	7	2
MYDRIASIS	1	0	0	0
PAROSMIA	0	5	3	1
TASTE COMMENTS	39	8	29	21
SPECIAL SENSES OTHER, DISORDERS TOTAL	40	13	32	22
AGGRESSIVE REACTION	1	0	1	0
AGITATION	6	3	4	2
ANOREXIA	2	1	2	1
ANXIETY	64	18	76	24
APATHY	1	1	1	0
CONCENTRATION IMPAIRED	8	2	1	4
CONFUSION	3	1	4	1
DEPERSONALIZATION	1	0	0	0
DEPRESSION	11	4	12	11
DREAMING ABNORMAL	1	2	1	5
DRUG DEPENDENCE	1	3	2	4
EMOTIONAL LABILITY	4	1	2	2
FATIGUE	6	3	8	6
HYSTERIA	0	0	1	0
INSOMNIA	7	8	12	9
NERVOUSNESS	9	2	12	6
NEUROSIS	3	0	0	2
PARONIRIA	3	0	0	0
PERSONALITY DISORDER	0	0	1	0
SLEEP DISORDER	5	2	1	5
SOMNOLENCE	3	0	4	3
SUICIDE ATTEMPT	1	0	0	0
THINKING ABNORMAL	0	0	0	1
WITHDRAWAL SYNDROME	12	4	7	7
YAWNING	0	0	0	1
PSYCHIATRIC DISORDERS TOTAL	152	55	152	94

Adverse Events by Body System in the Controlled Clinical Trials

	Plc-Smk	Plc-Qt	Act-Smk	Act-Qt
ABDOMINAL PAIN	15	7	11	8
COLITIS	0	1	0	0
CONSTIPATION	16	6	13	9
DIARRHEA	13	6	21	10
DIVERTICULITIS	0	1	1	0
DYSPEPSIA	35	22	56	44
DYSPHAGIA	0	0	1	0
ERUCTATION	0	1	2	2
FLATULENCE	10	7	20	11
GASTRIC ULCER	3	0	1	3
GASTRITIS	3	1	0	2
GASTRO INTESTINAL DISORDER NOS	0	0	1	0
GINGIVITIS	0	1	3	5
GLOSSITIS	1	2	5	1
GUM HYPERPLASIA	0	2	2	0
HALITOSIS	2	0	0	1
HICCUP	1	0	7	7
MOUTH DRY	28	17	27	28
NAUSEA	34	13	54	19
NAUSEA/VOMITING	2	0	2	0
ESOPHAGITIS	0	1	1	0
PEPTIC ULCER	1	4	0	0
SALIVA INCREASED	6	0	1	0
SALIVARY GLAND ENLARGEMENT	0	0	1	0
STOMATITIS	45	22	81	57
TEETH GRINDING	1	0	0	0
THROAT IRRITATION	38	13	111	67
TONGUE ULCERATION	1	1	3	1
TOOTH DISORDER	19	11	17	12
VOMITING	3	0	11	3
GASTRO INTESTINAL SYSTEM DISORD. TOTAL	277	139	453	290
CHOLELITHIASIS	1	0	0	0
HEPATITIS	0	0	0	1
LIVER AND BILIARY SYSTEM DISORD. TOTAL	1	0	0	1
APPETITE INCREASED	6	2	1	2
DEHYDRATION	1	0	0	1
HYPOTHYROIDISM	0	1	0	0
METABOLIC AND NUTRITIONAL DISORD. TOTAL:	289	142	465	298
OBESITY	1	1	1	0
EDEMA DEPENDENT	14	7	9	8
THIRST	3	3	8	4
WEIGHT DECREASE	0	0	1	0
WEIGHT INCREASE	1	2	1	2
ENDOCRINE DISORDERS TOTAL	19	13	20	14

Adverse Events by Body System in the Controlled Clinical Trials

	Plc-Smk	Plc-Qt	Act-Smk	Act-Qt
ANEURYSM	0	0	0	1
CEREBROVASCULAR DISORDER	0	0	1	0
HEART VALVE DISORDERS	0	0	0	1
HYPERTENSION	2	7	3	5
HYPOTENSION	1	0	0	0
CARDIOVASCULAR DISORDERS, GENERAL TOTAL	3	7	4	7
ANGINA PECTORIS	0	1	0	0
MYO , ENDO , PERICARDIAL & VALVE DISORD	0	1	0	0
ARRHYTHMIA	0	0	1	0
PALPATION	2	0	4	3
TACHYCARDIA	1	0	0	3
HEART RATE AND RHYTHM DISORDERS TOTAL	3	0	5	6
ARTERIOSCLEROSIS	0	0	0	1
ATHEROSCLEROSIS	0	0	0	1
HEMORRHOIDS	0	1	0	0
VASCULAR DISORDER	1	0	2	1
VEIN DISORDER	0	0	1	0
VASCULAR (EXTRACARDIAC) DISORDERS TOTAL	1	1	3	3
ASTHMA	0	2	1	1
BRONCHITIS	10	1	10	6
BRONCHOSPASM	1	1	2	1
CHEST PAIN	14	7	20	15
CHOKING	1	0	2	1
COUGHING	52	10	125	74
DYSPNOEA	6	4	8	6
HEMOPTYSIS	2	0	0	0
HYPERVENTILATION	0	0	0	1
LARYNGITIS	4	0	4	0
PHARYNGITIS	36	23	67	44
PLEURAL PAIN	0	0	2	0
PNEUMONIA	2	1	6	0
PNEUMONITIS	1	2	2	0
PULMONARY CARCINOMA	0	0	0	1
RESPIRATORY DISORDER	0	0	1	0
RHINITIS	74	21	83	54
SINUSITIS	27	23	36	22
SPUTUM INCREASED	1	3	3	1
UPPER RESP TRACT INFECTION	4	3	1	2
RESPIRATORY SYSTEM DISORDERS TOTAL	235	101	373	229
ANEMIA	0	0	1	0
HEMORRHAGE NOS	0	1	0	0
RED BLOOD CELL DISORDERS TOTAL	0	1	1	0
LYMPHADENOPATHY	2	1	3	2
WHITE CELL AND R.E.S. DISORDERS TOTAL	2	1	3	2
EPISTAXIS	2	3	6	5
GINGIVAL BLEEDING	0	1	3	5
PLATELET, BLEEDING & CLOTTING DISORDERS	2	4	9	10

Adverse Events by Body System in the Controlled Clinical Trials

	Plc-Smk	Plc-Qt	Act-Smk	Act-Qt
CYSTITIS	1	1	2	1
NEPHRITIS	2	0	1	1
POLYURIA	0	0	1	1
RENAL FUNCTION ABNORMAL	0	0	0	1
URINARY TRACT INFECTION	0	1	1	5
URINARY SYSTEM DISORDERS TOTAL	3	2	5	9
BREAST DISCHARGE	1	1	1	0
DYSMENORRHEA	7	5	11	8
ENDOMETRIOSIS	1	0	0	0
INTERMENSTRUAL BLEEDING	1	0	0	0
MENOPAUSAL SYNDROME	0	0	0	2
MENORRHAGIA	0	0	2	0
MENSTRUAL DISORDER	2	4	8	1
PREGNANCY ECTOPIC	0	0	0	1
PREMENSTRUAL TENSION	2	0	3	1
VAGINITIS	0	0	1	0
REPRODUCTIVE DISORDERS, FEMALE TOTAL	14	10	26	13
HERNIA CONGENITAL	0	0	1	0
FETAL DISORDERS TOTAL	0	0	1	0
BREAST NEOPLASM FEMALE	0	0	1	0
OVARIAN CYST	1	0	0	0
NEOPLASM TOTAL	1	0	1	0
ABDOMEN ENLARGED	0	1	0	0
ALLERGIC REACTION	2	0	1	1
ALLERGY	8	2	14	7
ASTHENIA	1	0	2	0
CARPAL TUNNEL SYNDROME	1	1	0	0
CRYING ABNORMAL	1	0	1	0
FACE EDEMA	0	0	2	1
FEVER	6	4	8	8
HOT FLUSHES	3	1	3	2
INFLUENZA LIKE SYMPTOMS	23	8	21	20
MALAISE	3	2	4	1
EDEMA	14	7	9	8
PAIN	28	17	23	28
RIGORS	7	1	7	2
THERAPEUTIC RESPONSE DECREASED	8	1	0	2
BODY AS A WHOLE GENERAL DISORDERS TOTAL	105	45	95	80
CELLULITIS	1	0	0	0
APPLICATION SITE DISORDERS TOTAL	1	0	0	0
ABSCESS	1	0	0	0
HERPES	1	1	3	4
INFECTION	11	6	10	8
MONILIASIS	1	1	0	0
OTITIS MEDIA	1	1	1	0
RESISTANCE MECHANISM DISORDERS TOTAL	15	9	14	12
FAMILY STRESS	3	0	2	0
SECONDARY TERMS TOTAL	3	0	2	0
ACCIDENT	1	0	0	2
INSUFFICIENT	30	10	26	19
PRACTICAL PROBLEMS	10	4	6	2
BODY SYSTEM UNKNOWN TOTAL	41	14	32	23

NDA 20-714

cc:
Orig. NDA 20-714
Div. File
HFD-170/Kramer/Ross/Doddapaneni/Geyer/Permutt/McNeal
HFD-344

Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel:(301)443-3741

MEDICAL OFFICER REVIEW

NDA: 20-714 SERIAL # 008
SPONSOR: Pharmacia and Upjohn Company
DRUG: Nicotine inhalation system
TYPE OF SUBMISSION: **Safety Update, Study Report**
PROPOSED INDICATION: Smoking Cessation
MEDICAL OFFICER: AW Longmire
PEER MEDICAL OFFICER: C Winchell
LETTER DATE BY SPONSOR: 04/07/97
DATE RECEIVED BY CDER: 4-11-97
DATE REVIEW COMPLETED: 04/28/97
REGULATORY ACTION: Approval Anticipated
CSO: E McNeal

GENERAL INFORMATION (Key Words)
PHARMACOLOGY CATEGORY: Nicotine Replacement Therapy
ROUTE OF ADMINISTRATION: PO
STUDY TITLE: Assesment of the risks associated with Improper use of Nicotrol Inhaler in children. A safety study
PRINCIPAL INVESTIGATOR: E Lunell
PROTOCOL #: 96NNIN021
STUDY LOCATION: Sweden
CONTROL (OTHER) DRUGS: NA

Background
The approval decision PDUFA date of this project is Friday May 2, 1997.

Abstract
This submission contains a response to chemistry (forwarded to chemistry) and a safety update of pertinent information obtained from clinical studies, post-marketing experience and the scientific literature during the time period January 1 1996 through March 25, 1997. It also contains the final study report for Clinical Study 96NNIN021, entitled "Assesment of the risks associated with improper use of Nicotrol Inhaler in children. A safety study" (forwarded to PK). This review is on the safety update and the safety aspects of study 96NINN021.

Safety Update
January 1,1996 - March 25, 1997

Nicotrol Inhaler was launched in Denmark in September 1996, Sweden in December 1996, and Italy in February 1997. This report is from clinical trials, post-marketing experience, and a review of the scientific literature. The reports include all serious reports (by FDA criteria). Three adverse drug events, two from clinical trials and one from Post-marketing experience, are reported.

CLINICAL TRIALS

1. Patient No. , clinical Trial 95NNIN012 (France)

A 59-year old female smoker of 42 years using Nicotrol Inhaler and patches for smoking cessation developed a hepatic neoplasm and the study treatment was discontinued. The patient had a history of respiratory problems. The investigator assessed the hepatic neoplasm as unrelated to Nicotrol Inhaler use.

2. Patient No clinical Trial 95NNIN012 (France)

A 44-year old male with a smoking history of 29 years was hospitalized for an unspecified surgery while receiving Nicotrol Inhaler and nicotine patch. The patient had a history of depression, peptic ulcer, morning cough, shortness of breath, and asthma. The clinical investigator has no official information regarding the surgery, "Further information is being sought."

CASE REPORTS FROM POST-MARKETING EXPERIENCE

A 61-year old female took between 20 - 30 inhalations of the inhaler, equivalent to 2 mg nicotine, after leaving work due to illness. She subsequently developed dizziness and loss of consciousness She was referred to intensive care where she developed ventricular fibrillation. Cardioversion was performed and she reverted to normal sinus rhythm. ECG revealed ischemic heart disease. She was observed for a short time and released in good condition. This woman had a history of previous myocardial infarction and heart failure. The event was assessed as unrelated to Nicotrol Inhaler use.

REVIEW OF SCIENTIFIC LITERATURE

No case reports of the nature described above were reported in the scientific literature during the time period of the safety update.

Discussion

These events would seem unlikely to be related to the Nicotrol Inhaler.

PROTOCOL # 96NNIN021

Assesment of the risks associated with Improper use of Nicotrol Inhaler in children. A safety study

This report was reviewed by PK, I will comment on safety aspects of the study. The study was done in 7 adult snuff users who placed the nicotine porous plug in their mouth for 1 minute. About 1.2 mg of nicotine was released. Maximum mean plasma levels of 6 +/- 4 ng/ml (range) occurred at 5 minutes; this would extrapolate to 24 ng/ml (range) for a 10 kg child. The maximum pulse rate reported was 84, the maximum BP recorded was 157 /84. One subject reported moderate dizziness and another reported local anesthesia and heartburn.

Discussion

The division is currently in negotiation with the sponsor on phase IV childproofing of this product and labeling. This study does not indicate unacceptable risk.

Regulatory Action:
NAI

A Longmire 9/3/97
Medical Review Officer

C Winchell
Group leader, PEER Review Officer
CC: Original IND
HFD-170 Division File
HFD-170 CSO E McNeal
HFD-170 AW Longmire
HFD-170 C Winchell
HFD-170 C Wright