CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-612/S022

20-066/S004

MEDICAL REVIEW

27.1

SEP - 7 1995

Medical Officer's Review:

Applicant:	Marion Merrell Dow
NDA No:	20-066, S-004 [redacted] 18-612/S022
Product:	Nicorette DS, Nicorette
Indication:	Smoking Cessation
Date Received:	August 15, 1995
Date Reviewed:	August 31, 1995
Date Completed:	September 7, 1995

Introduction:

This a review of the Postmarketing Surveillance Plan for OTC Nicorette and the Postmarketing Intervention/Action Plan. There is concern that wider access to nicotine containing products with OTC availability of Nicorette, specifically with regard to misuse among those less than 18 years old. The sponsor had provided a discussion of the various ways that Nicorette could potentially be misused, such as:

- extended use
- off-label use, including, concomitant smoking and Nicorette use, use of Nicorette by nonsmokers, use of Nicorette for specific effects, use by teens/adolescents
- accidental child exposure
- abuse

In a previous submission dated July 1, 1995, the sponsor had outlined their marketing approach to OTC Nicorette which is summed up as follows:

- target population: committed quitters
- advertising focus: quitting is not easy but can be achieved; adults targeted, no advertising on children's shows, etc
- distribution: retail incentive to shelve with other OTC drugs, no vending machine or convenience store sales
- child proof packaging, no free samples or low-priced trial/travel packs
- educational programs: via media, Committed Quitters Program

Surveillance Program:

In this current submission, the sponsor has described a Postmarketing Surveillance Program. Components of the surveillance program are targeted to identify special issues which may be associated with the OTC environment, such as drug misuse, rather than seious adverse events. The following components were listed:

(1) Spontaneous Reporting via the 800 telephone number
(2) Committed Quitters Program
(3) Consumer Tracking via random-dial telephone interviews
(4) Theft Surveillance via reporting by retail store managers and buyers
(5) Media Monitoring via online monitoring of media databases, news clipping service, and broadcast coverage

(6) American Association of Poison Control Centers (AAPCC)
(7) Drug Abuse Warning Network (DAWN)
(8) Addiction Center Survey
(9) National Household Survey on Drug Abuse (NHSDA)
(10) Monitoring the Future (MTF) Survey
(11) Parents Resource Institute for Drug Education (PRIDE) Survey
(12) Survey of Drug Free Schools Coordinators

Medical Officer's Comments:

While this is a conscientious effort on the part of the sponsor to track consumer use of Nicorette post OTC-switch, it may be unreasonable to expect too much from these sources by way of early signals for misuse. The majority of information obtained via (1), (2), (3), and (6) is probably related to questions about using/stopping Nicorette, side effects with Nicorette use, accidental overdoses. It is unlikely to be an early signal for teenage misuse, for example. The MTF and PRIDE surveys and the NHSDA do not have questions on Nicorette use specifically. The yield from a survey of drug abuse treatment center personnel is also expected to be low since it is unclear if Nicorette use is ever addressed. Data from DAWN may be useful for trends over time but is not as useful for picking up current events. Furthermore, DAWN's major focus is on drugs of abuse. In order to get information on Nicorette mentions in the DAWN database, special data runs would have to be done.[1] All of the national surveys also do not have the capability to pinpoint increased misuse at the local community levels at the time of occurrence, which is essential for intervention to be implemented.

It may be optimistic to expect that new questions on Nicorette use could be included in the national surveys within a reasonable timeframe. It would appear then, that the most sensitive means of being alerted to 'epidemics' of Nicorette misuse would be through media reports of such occurrences, or through theft surveillance at the retail level. PRIDE, which does not have a probability sample, but does have a large sample (approximately 200,000) and surveys subjects in the appropriate age groups (grades 4 to 12), would be an appropriate survey to work with. PRIDE's president, Dr. Gleaton, mentioned that PRIDE is amenable to working with companies to add specific quesitons to their questionnaire. They may also have the capability to target specific localities.

The survey of drug free school coordinators may be helpful, provided that these coordinators are actually collecting or have access to information about drug use in their schools. If this survey is intended for surveillance purposes, the survey should be carried out on an ongoing basis rather than once at the 12 months post-launch period as suggested by the sponsor.

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[1] There were no mentions of Nicorette in DAWN for the period January 1991 to December 1993. **Special Run, DAWN 1991-1993, Office of Applied Studies, Substance Abuse and Mental Health Services Administration.**

Postmarketing Intervention/Action Plan

The sponsor also included an intervention/action plan that could be implemented under two possible scenarios. In the first instance, community level episode of teen misuse was detected via Media Tracking. An independent research company, —— would then be sent to the community to conduct in-depth interviews with informants to assess the nature of the misuse and determine its causative factors. Based on the assessment, the sponsor would take specific actions to remedy the situation. These actions may include: changes in advertising, promotional, and retail practices, changes in product labeling, and a community/school-based educational program.

In the second scenario, the 800 number picks up a consumer who is having trouble stopping Nicorette. The consumer is helped with the weaning process via telephone and mail contact, and is ultimately encouraged to see a physician/health professional.

Medical Officer's Comments:

Both scenarios may actually reflect what would most likely happen, should there be Nicorette misuse. Media Tracking may indeed be the earliest and most sensitive of all of the monitoring methods listed in the surveillance plan. This does depend in large part on how much of the nation's news media, including local media, is covered by Media Tracking, and the frequency and repetitiveness of the search for Nicorette news. The sponsor's plan to have a research company available (with past experience with community-level dextromethorphan abuse) to respond to the misuse event is key to being able to mobilize and assess the nature of the problem. The next step is to have some ideas of what possible interventions could be implemented given the nature of the problem. The list of specific actions also appear reasonable. The critical element is in having an ability to pick up community level events as they occur and to have an action plan to tackle the problem while it is still confined to the community, rather than waiting for the lag time in national surveys before picking up a national trend of problematic Nicorette use.

The second scenario of the consumer having extended use of Nicorette also appears to be dealt with appropriately. The sponsor appeared willing to provide support via the Committed Quitters Program, continued phone and mail contact, with ultimate referral to a physician or health care personnel if the consumer remained unsuccessful with stopping Nicorette use.

Conclusions:

While there is concern about Nicorette misuse, especially among teens, there is no current knowledge about whether or not teen misuse will be a major problem should Nicorette become available OTC. The sponsor has outlined a responsible marketing approach in targeting committed quitters, while refraining from practices that would make Nicorette attractive to teen use. They have also proposed a surveillance and action plan to address OTC safety and misuse concerns. Given that existing data systems fall short of being sensitive enough to detecting misuse problems at the community level as they occur, the approach of using the media and a research company seems to provide the next best available solutions. The sponsor may need to

explore other options, e.g. PRIDE, for continuous, long-term monitoring. It may be that PRIDE surveys could be initiated and continued in areas where the problem is identified; to describe the episode and to monitor for improvement or worsening of the problem over time. If the problem appears to have resolved, the surveys could then be discontinued. The sponsor can also build into their existing systems of the 800 number, Committed Quitters Program, and consumer tracking surveys, heightened awareness of the ability to report Nicorette misuse to these resources rather than just question/side effects type of consumer concerns.

Ling Chin, M.D., M.P.H.
Medical Officer

Peer reviewer comments: The applicant has outlined standard routes of obtaining ADR-related and overdose information in the AAPCC and MedWatch systems. However, additional tracking and/or surveillance systems which appear likely to provide *early signal* information after the product is made available OTC have also been proposed. These proposals have not yet been provided in sufficient detail to completely evaluate them; however, we agree in concept that some of these sources may provide critical information needed to redirect advertising, labeling, and/or promotion of the product in case of misuse.

1) Media monitoring: Extensive tracking and monitoring of media reports along with specific followup by an objective interview research group appears to be a very promising early mechanism for tracking misuse.

2) The 800 number spontaneous reporting is a potential source of invaluable information. It could be enhanced to obtain early signal information by providing a list of questions to persons answering this phone which could be asked whenever misuse is reported or suspected.

3) Obtaining information from drug-free school counselors or program administrators on a repeat basis using standardized questions may provide helpful information.

4) Theft surveillance: Identifying who steals and why may result in followup information which leads to an *early signal* regarding misuse potential.

5) Although there is no probability sample in PRIDE the sample is large. Thus, this survey might also prove helpful for monitoring potential misuse in children since it samples children from grades 4-12 (i.e., 9-18 y.o.).

Through: Debra Bowen

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AUG - 7 1995

Medical-Statistical Review

NDA:	18612 [redacted] 20066
	Nicorette, 2mg & 4mg
Sponsor:	Marion Merrell Dow
Study:	NIPR0013
Submitted:	December, 1994
Primary Reviewers:	E Douglas Kramer, MD
	Thomas Permutt, PhD
Secondary Reviewers:	Curtis Wright, MD, MPH
	Hoi Leung, PhD
CSO:	Sharon Schmidt
File:	c:\data\nicorett\reviews\ni13rev1.doc

A 12 Month Follow-Up Study Evaluating Smoking Cessation After Completing The Nicorette OTC Usage Studies NIPR0009 And NIPR0012

Abstract:

Subjects completing the 12 week Nicorette OTC usage studies were eligible to participate in this study if they reported that they were not smoking regularly at 12 weeks and had an expired CO<=10ppm. Subjects were contacted by telephone at 6 months and again at 12 months if they continued to be abstinent. Those who reported that they were not smoking were asked to have an expired CO determination. Among 2981 subjects enrolled in the usage trials, 1005 were eligible to participate in this trial and 780 (78%) did so. Among subjects who had been enrolled in Study 9, quit rates at 6 and 12 months were 9% and 7% respectively. Among subjects who had been enrolled in study 12, quit rates at 6 and 12 months were 6% and 5% respectively. In both studies, 3% of subjects reported still using gum at 12 months and 2% said they had used gum continuously since the 6 month visit.

Protocol:

Subjects who attended the 12 week visit and who reported not smoking regularly and had expired CO<=10 were eligible to participate. Gum was not available for purchase during this study, but participants could obtain it from a physician (either the investigator or their private physician) by prescription. Enrolled subjects were contacted by phone for an interview to determine smoking status at 6 months. Those who were not smoking were asked to take a CO test for verification. Subjects who were not smoking at 6 months were contacted again at 12 months for verification of smoking status. Spontaneously reported adverse events were noted for those subjects using Nicorette at the time of the event.

The protocol was amended 3 times. The first amendment was to allow the study to follow only those subjects who were nonsmokers. The second amendment was to allow the study to follow only nonsmokers after the 6 month visit. As in the original usage studies, the sponsor asked the subjects whether they were smoking and when they started smoking, not whether they had smoked at all. In an effort to determine continuous quit rates, the third protocol amendment was to determine continuous abstinence from 12 weeks at the 12 month visit.

Results:

From study 9, 876 subjects were eligible for follow-up. From this study, 707 subjects agreed to participate, including 19 subjects who did not meet all abstinence requirements. From study 12, 129 subjects were eligible for follow-up and 92 subjects agreed to enroll, all of whom were eligible. Overall participation in this trial was 780/1005 (78%) of eligible subjects.

Abstinence:

Because both usage trials measured continuous abstinence at 6 weeks and current abstinence at 12 weeks, 6 months, and 12 months the following definition of abstinence was used by the reviewers: subjects were considered abstinent at 6 and 12 months if they were abstinent continuously at 6 weeks, reported not smoking regularly at 12 weeks and reported not smoking at the follow-up visits. Abstinence at 6 and 12 months (verified by expired CO) is given in the following table:

Long-Term Abstinence

Study	6 Month Verified Abstinence	12 Month Verified Abstinence
Study 9 N=2590	228 (9%)	184 (7%)
Study 12 N=391	25 (6%)	18 (5%)

Figures are N (%). Table made by the reviewers from the Sponsor's electronic data set. Abstinence is as defined in the text above. Continuous abstinence since week 12 reported at the 1 year follow-up was 1% lower.

Use of Gum:

Gum was not provided in this study, but subjects were free to obtain it by prescription if they wished. At study visits, subjects were asked if they had used gum since the last visit, if they were still using gum, and if so were they using it continuously. Continued use of Nicorette is listed in the following table:

Gum Use Beyond 3 Months

Study	**Gum Use At 6 Months** Any Use Since Last Visit Still Using Continuous Use N (%)	**12 Month Gum Use** Any Use Since Last Visit Still Using Continuous Use N(%)
Study 9 N=2590	325 (13%) 160 (6%) 92 (3%)	156(6%) 85 (3%) 40 (2%)
Study 12 N=391	42 (11%) 17 (4%) 9 (2%)	19 (5%) 13 (3%) 7 (2%)

Table made by the reviewers from the sponsor's electronic data set. Results are N (%). Based on all subjects enrolled.

Among 156 subjects from study 9 who reported any gum use during the last 6 months of follow-up, 115 were using 2mg gum, 38 were using 4mg gum and 3 used both strengths. Fifty subjects had switched from 4mg at the beginning of Study 9 to 2 mg by 12 months and 3 subjects switched from 2mg gum at the beginning to 4mg gum at 12 months.

Among 19 subjects from study 12 who reported any gum use during the last 6 months of follow-up, 13 were using 2mg gum, 5 were using 4mg gum and 1 used both strengths. Five subjects had switched from 4mg at the beginning of the usage trial to 2 mg by 12 months and 1 subject switched from 2mg gum at the beginning to 4mg gum at 12 months.

Adverse Events:

Adverse events volunteered by subjects were recorded if the subject had used Nicorette with 24 hours of the event. Seven adverse events were recorded for 5 subjects. Notable events included:

A 66 year old woman with no significant medical history was hospitalized for chest pain felt to be related to coronary artery disease. An ascending aortic aneurysm was also found at evaluation. She was rehospitalized 6 months later with abdominal pain. Evaluation revealed a sliding hiatal hernia gastroesophageal reflux, gastritis and a bleeding ulcer. She had quit smoking in study 9 using 4 mg gum. She continued to use 2mg gum (from her private physician) throughout follow-up and remained a nonsmoker (2 mg pieces cut in quarters). The investigator felt that the chest pain was possibly related to Nicorette but the GI complaints were not likely to be related to gum use.

A 65 year old man with a history of peptic ulcer since 1987 was being treated with Zantac when he complained of black stools for 24 hours. This was a chronic problem for which the patient was instructed by his physician to double his Zantac dose. He was using 4 pieces of 4mg gum/day at the time and his therapy was unchanged. The investigator felt that this subject's GI events were not likely to be related to Nicorette.

While these events are possibly related to Nicorette use, it is difficult to attribute them to Nicorette rather than to pre-existing conditions.

A pregnancy that resulted in the birth of healthy twin boys. She had used 2mg Nicorette 1 or 2 pieces/day for the first 2 weeks of her pregnancy.

Conclusions:

Long-term smoking cessation rates in these studies were 5% to 7% at 1 year.

Use of gum was reported by 3% of subjects at 1 year, with 2% reporting continuous use. This is consistent with the previous observations that some smokers may use the gum for longer periods than recommended. However, the pattern of long-term use showed a gradual reduction in the strength of gum chosen over time, with no evidence of tolerance development or reports of addictive behavior.

The serious or potentially serious adverse events in this trial are part of the labeled precautions for use of prescriptive Nicorette. It is difficult to attribute them to Nicorette rather than to pre-existing conditions.

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27.1

JUL 27 1995

Medical-Statistical Review

NDA:	20,066-S004 & [redacted] 18,612-S022
Sponsor:	Marion Merrell Dow
Drug Product:	Nicorette Gum (nicotine polacrilex)
Submitted:	December, ~~1994~~
Review Completed:	July 27, ~~1994~~ 1995
Study #:	NIPR0009
Primary Reviewers:	E Douglas Kramer, MD Thomas Permutt, PhD
Secondary Reviewers:	Curtis Wright, MD, MPH Hoi Leung, PhD
CSO:	Sharon Schmidt
File:	c::\data\nicorett\reviews\rev9fin4.rtf

Evaluation Of The Adequacy Of The Labeling To Assure The Safe And Effective Use Of Nicorette 2mg And 4 mg In An OTC Environment

Abstract: This was a 39-center, 12-week, open label usage study of nicotine polacrilex (Nicorette gum) in smoking cessation in an OTC environment with minimal intervention. Enrolled subjects were 2590 adults aged 18 to 80 who wanted to quit smoking who self-selected from media advertisements. Correct self-assessment of the need to see a doctor based on the label was 9 % among subjects who reported risk factors listed on the label and 96% among those with no reported risk factors. The low intent to heed the label for subjects with labeled conditions seemed to vary somewhat based on the conditions the subjects reported, but the overall rate may reflect the excessively reasssuring wording of the label tested. The correct gum dose was chosen by 91% of heavy smokers and 76% of light smokers. Self-reported quit rate at 6 weeks (verified by exhaled CO) was 17%, The adverse events most commonly observed for Nicorette were DSM III withdrawal symptoms followed by headache, GI complaints and mouth and tooth problems. Serious adverse events were likely attributable in whole or in part to intercurrent or pre-existing medical conditions or long term consequences of cigarette smoking.

Protocol:

Nicorette was available in an OTC setting under conditions of minimal medical intervention. The study was advertised in several local media and subjects went to the study site (a pharmacy or mall storefront) to learn more. To enroll in the study, subjects were asked to read either the 2 or 4 mg Nicorette gum labels; they could read both. Those who decided to purchase Nicorette on the basis of the labeling were asked questions about their smoking and health histories to determine their understanding of the label and the appropriateness of their choice.

All persons wishing to purchase gum (with the exception of pregnant or lactating women) were allowed to enter the study, regardless of whether they indicated the presence of a labeled risk factor. Subjects with labeled risk factors (e.g. recent heart attack, hypertension, diabetes requiring insulin, use of prescription medication etc.) were given permission to enter the study by the site investigator. This was done by a combination of specific decisions on a patient by patient basis and blanket waivers given by some investigators for conditions such as use of birth control pills and hypertension controlled by beta blockers.

Nicorette could be used for up to 12 weeks from the date of enrollment. Required visits were at 6 and 12 weeks for verification of abstinence and assessment of adverse events.

Nicorette was sold in boxes containing 96 pieces each and could be purchased at any time prior to the 12 week visit for $35/box ($30 with coupon). Subjects reporting to study sites between visits 6 and 12 to purchase additional gum had an additional adverse event assessment at the time of purchase. (Moneys collected were refunded to the subjects as a part of research payment fees to avoid pre-approval marketing).

Protocol Amendments:

The sponsor amended the protocol several times while the study was proceeding. Amendments included:

1. Provision for an intent to treat analysis;

2. Provision to use tent-cards at study sites to correct an oversight in the labeling of Nicorette boxes. The boxes as printed did not contain any instructions on gum choice for persons exactly 25 cigarettes/day. The tent cards recommended 4 mg gum for persons smoking ≥25 cigarettes/day.

3. The sponsor anticipated poor compliance with completing daily diaries early in the trial and amended the protocol to allow for the determination of abstinence just by the usual measure of self report and exhaled CO.

4. The protocol was amended several times regarding the inclusion of pregnant or lactating women.

These amendments are reasonable and consistent with divisional standards for the interpretation of smoking cessation trials.

Outcome Measures:

Appropriateness of subjects' decisions to purchase OTC Nicorette based on the label warnings regarding pre-existing medical conditions.

Appropriate selection of dose based on label recommendations (2mg gum for those smoking <25 cigarettes/day and 4mg gum for those smoking >=25 cigarettes/day).

Ability of participants to identify and make an appropriate response to adverse events in an OTC setting.

Ability of subjects to stop smoking for 30 consecutive days prior to the 6 week visit.

Study Sites:
The 46 locations for the 39 study sites included 12 market research offices, 9 shopping malls, 5 business office buildings, 5 research centers, 4 churches, 4 pharmacies, 3 work sites, 2 clinic/dental offices, 1 civic center and 1 athletic club. Sites enrolled from 8 to 300 subjects over an 8 week recruitment period.

Subject Screening:

A total of 3,125 candidates read the study label for this trial. Of these, 535 did not enroll in the study by purchasing Nicorette. Among subjects who did not enroll, 228 indicated only that they did not want to purchase Nicorette and a further 186 subjects (who did not enroll) offered reasons such as cost, health problems, or personal reasons for non-enrollment even though they said they would like to purchase the gum. Forty-seven candidates who did not enroll offered no reason for this decision, and no reason was captured by the study site. A total of 74 candidates who did not participate in the trial, may have been excluded by the study sites for reasons of health (N = 70), non-smoking status (N = 6), age (N = 2) or low CO (N=1).

Counting the 70 candidates who may have been excluded by study sites for medical reasons, the proportion of those with medical conditions who were allowed to enroll was >= 90% of all candidates with those conditions except for

those taking prescription medication for depression/asthma (83%), irregular heart beat (89%), diabetes (88%), recent heart attack (67%), and women breast-feeding (50%). A total of 16 sites enrolling a total of 1,091 subjects did not exclude any candidates for any medical reasons.

Demographics of Enrolled Subjects:

The choice of gum dose was left to the subjects , based on their understanding of the labeling. The 4 mg gum is recommended for those smoking >=25 cigarettes/day, while the 2mg gum was recommended for those smoking <25 cigarettes/day. The demographics of the 2587 patients who participated by self-selected dose (excluding the 3 subjects whose dose choice was not recorded) are described in the following table:

Characteristic	2mg Gum N=1009	4 mg Gum N=1578
Men (number)	349 (35%)	760 (48%)
Women (number)	659 (65%)	818 (52%)
Height (in) mean, SD, range	67 (4) (53-78)	68 (4) (53-80)
Weight (lb) mean, SD, range	154 (33) (91-290)	165 (37) (74-325)
Age (years) mean, SD, range	43 (12) (18-79)	45 (12) (18-80)
Years Smoking mean, SD, range	21 (12) (1-65)	25 (12) 0-63
Cigs/day mean, SD, range	18 (7.1) (0-60)	32 (11) (0-90)
Exhaled CO(ppm) mean, SD, range	22 (13) (0-87)	31 (16) (0-113)
Ever Tried to Quit	89%	89%
Used Gum or Patches Before	37%	42%
Used Other Programs	47%	52%
Ready to Stop Today	92%	92%
Reasons to Quit:		
Job	18%	20%
Family	45%	45%
Health	89%	89%
Cost	40%	44%
Laws	13%	14%
Other	7%	5%
Does Anyone Else in Your household Smoke? (% Yes)	35%	38%

Table made by the reviewers from the sponsor's electronic data set.

There are a number of differences between the dose groups in addition to the number of cigarettes smoked per day. These differences (e.g. in expired CO, weight, number of years smoking) are consistent with differences observed between heavier and lighter smokers in previous clinical trials of smoking cessation.

Ethnic background of subjects was white (90%), black (6%) and other (4%).

Efficacy:

To be considered abstinent at 6 weeks, subjects had to report not smoking for the last 30 days and have a confirmatory exhaled CO determination.

Efficacy in this study is given in the table below.

Subjects Abstinent At 6 Weeks

	6 Weeks
All Subjects (N=2590)	17%
2mg Gum (N=1009)	18%
4mg Gum (N=1578)	16%

Quit rates varied from 4 - 38% among 39 study sites.

Subjects who stopped smoking had somewhat lower baseline CO levels and tended to report smoking fewer cigarettes at baseline than those who did not. In keeping with other smoking cessation trials, quit rates vary considerably among centers.

Six week quit rates did not vary appreciably by sex or race. The quit rate for women was 17%, for men 16 %, for black participants, 18%, and 15% for other non-white subjects. The quit rate was 22% among 260 subjects>60 years of age.

Subjects were considered abstinent at 12 weeks if they reported they were not 'smoking regularly' and if they had a confirmatory CO determination. At 12 weeks, 541 subjects (21%) claimed not to be smoking for at least 7 days. This included 302 of 432 subjects (70%) who were abstinent at week 6.

Safety:

The safety database for this trial was assessed in three ways: Subjects were asked specifically whether they experienced any nicotine withdrawal symptoms listed in DSM III R. In addition, subjects were queried about adverse events by site personnel when they returned to the study site. The sponsor also audited available subject diaries in assembling the adverse event dataset.

Withdrawal:

Withdrawal symptoms were the most commonly reported adverse events in this study.

Nicotine Withdrawal Symptoms By Dose Group At 6 Weeks

	% Reporting Symptoms At Or Before Week 6	
Symptom	2mg Gum N=850	4mg Gum N=1283
Craving	38	36
Irritability	25	23
Restlessness	21	20
Anxiety	21	23
Increased Appetite	18	17
Difficulty Concentrating	9	11
Decreased Heart Rate	2	1

Based on the number of subjects in each dose group who attended the clinic for the 6 week visit. Percentages are based on those who reported experiencing each withdrawal symptom in the previous 6 weeks. Figures include adverse events receded as withdrawal symptoms by the sponsor. Ten subjects on 2mg gum and 15 subjects on 4mg gum did not respond to this question. Assuming that these subjects each experienced all 7 withdrawal symptoms would increase the prevalence of each withdrawal symptom by 1%

Serious Adverse Events:

A total of 16 subjects experienced serious adverse events in this trial. This included 6 hospitalizations for intercurrent infection, 3 hospitalizations for exacerbations of pre-existing conditions, 3 MI's (one in a subject who never used gum), 2 accidents, 1 peripheral vascular thrombosis, and 1 possible pulmonary embolism. Some of these events are not unexpected in a population of smokers (e.g. bronchitis). Others (e.g. myocardial infarction) may be related to smoking or to the stress of attempting to quit smoking. The 16 serious adverse events reported in this study are listed in the table below:

Serious Adverse Events:

Age Sex	Dose Duration	Event	Rx
62 Male	4mg 8 days	Hospitalized with recurrent bronchitis; on steroids and inhaler prior to study	Continued
39 Male	4mg 80 days	Hospitalized for recurrent migraine headache with neurologic symptoms	Discontinued
39 Male	2mg 9 days	Hospitalized for viral meningitis	Continued
51 Female	2mg 40 days	Hospitalized for asthma. Previously on theophylline, steroids, albuterol	Continued
49 Female	2mg 42 days	Hospitalized for flare of Multiple Sclerosis	Continued
45 Male	4mg 66 days	Hospitalized for MI 3 weeks. History of High Cholesterol, emphysema, angina	Discontinued
66 Male	4mg 37 days	Hospitalized for arterial thrombosis of left leg requiring bypass	Continued
35 Male	4mg 57 days	Hospitalized for MI. Positive family history. Continued to smoke while on gum.	Discontinued
41 Male	2mg 27 days	Hospitalized for resection of tumor behind thyroid	Discontinued prior to event
35 Male	4mg 41 days	Hospitalized following auto accident [had seizure while driving].	Continued
40 male	2mg 38 days	Hospitalized for pneumonia	Discontinued later resumed
40 Female	4mg 49 days	Hospitalized for pneumonia	Discontinued later resumed
36 Female	4mg 35 days	Hospitalized for UTI	Continued
46 Female	4mg 26 days	History of eosinophilic fascitis, thyroid disorder, arrythmia. Hospitalized for CHF with possible pulmonary embolus.	Continued
63 Female	4mg 16 days	Hospitalized with wrist fracture	Continued
53 Male	4mg 45 days	Hospitalized for removal of infected plate in skull	Continued

Nonserious Adverse Events:

A total of 4663 adverse events were reported by a total of 1464 subjects during this study. Of these, a total of 4613 nonserious adverse events were reported by 1448 subjects who experienced only nonserious adverse events and 50 events were reported by 16 subjects who reported both serious and nonserious adverse events.

The frequency of the 180 classes of adverse events reported by the 1448 subjects who reported only nonserious adverse events is given in the Table 1 of the Safety Appendix.

To analyze nonserious adverse events: 1] Adverse events recorded as withdrawal symptoms on the CRF checklist were removed, leaving a total of 4163 adverse events and 2] Duplicate mentions of the same adverse event in the same subject were removed, leaving a total of 3305 unique adverse events reported by 1410 subjects. The frequency of these events is given in Table 2 of the Safety Appendix.

To further reduce the data set the following items were removed from the data set:

Adverse events considered intercurrent infections were removed (Sponsor's code='RESISTANCE MECHANISM').

Pulmonary disorders common in smokers were removed regardless of frequency (Sponsor's Code= 'RESPIRATORY SYSTEM') except for throat irritation and sinusitis which occurred frequently and were considered potentially local effects of Nicorette use.

The following non-cardiac, non-gastrointestinal, non-oral non-serious low-frequency (<1%) adverse events were removed (listed by sponsor's body system code):

BODY AS A WHOLE, except for reports of Pain that referred to Jaw Pain, Medical Procedure that referred to dental extractions, or Fatigue, a possible withdrawal symptom and 1 report of Generalized Edema, a possible cardiac event.

CENTRAL & PERIPHERAL NERVOUS SYSTEM except for Headache and Dizziness which were frequent enough to be considered possibly related to Nicorette use

ENDOCRINE, METABOLIC & NUTRITIONAL, MUSCULOSKELETAL SYSTEM, REPRODUCTIVE - FEMALE, URINARY SYSTEM, SKIN & APPENDAGES (except for Sweating Increased, a possible symptom of withdrawal or intoxication), VASCULAR–EXTRACARDIAC (e.g. hot flushes), and VISION adverse events were removed.

With the exception of Back Pain the frequency of reported adverse events in these categories was <1%. Ear and hearing disorders (mostly earaches, total frequency <1%) were also removed.

In addition the following adverse events were combined into single categories:

All PSYCHIATRIC adverse events (including insomnia and depression with a total of 116 reports).

MOUTH/TOOTH DISORDERS with a frequency of <1%

GASTROINTESTINAL SYSTEM DISORDERS with a frequency of <1%

This left the following reduced table of 2401 unique occurrences of 31 adverse events reported by 981 subjects which were either commonly observed and/or likely to be related to gum use and/or nicotine consumption

Nonserious Adverse Events Likely to Be Related to Gum Use

Sponsor's Body System Classification	Sponsor's Preferred Term	Prevalence
CENTR & PERIPH NERVOUS SYSTEM	HEADACHE	17%
GASTRO-INTESTINAL SYSTEM	NAUSEA	10%
GASTRO-INTESTINAL SYSTEM	DYSPEPSIA	9%
GASTRO-INTESTINAL SYSTEM	HICCUP	7%
RESPIRATORY SYSTEM	THROAT IRRITATION	6%
PSYCHIATRIC	PSYCH	6%
CENTR & PERIPH NERVOUS SYSTEM	DIZZINESS	5%
GASTRO-INTESTINAL SYSTEM	GASTRO-INTESTINAL OTHER	5%
MOUTH/TOOTH DISORDERS	TOOTH DISORDER	4%
MOUTH/TOOTH DISORDERS	STOMATITIS	4%
BODY AS A WHOLE	FATIGUE	3%
MOUTH/TOOTH DISORDERS	TASTE PERVERSION	3%
RESPIRATORY SYSTEM	SINUSITIS	2%
BODY AS A WHOLE	JAWPAIN	2%
MOUTH/TOOTH DISORDERS	STOMATITIS APHTHOUS	2%
GASTRO-INTESTINAL SYSTEM	ABDOMINAL PAIN	2%
GASTRO-INTESTINAL SYSTEM	CONSTIPATION	1%
MOUTH/TOOTH DISORDERS	GINGIVITIS	1%
MOUTH/TOOTH DISORDERS	GLOSSITIS	1%
AUTONOMIC NERVOUS SYSTEM	DRY MOUTH	1%
CARDIOVASCULAR- GENERAL	CHEST PAIN	1%
MOUTH/TOOTH DISORDERS	TONGUE ULCERATION	1%
BODY AS A WHOLE	DENTAL EXTR	<1%
MOUTH/TOOTH DISORDERS	MOUTH/TOOTH OTHER	<1%
SKIN & APPENDAGES	SWEATING INCREASED	<1%
CARDIOVASCULAR- GENERAL	HYPERTENSION	<1%
HEART RATE & RHYTHM	TACHYCARDIA	<1%
HEART RATE & RHYTHM	PALPITATION	<1%
CARDIOVASCULAR- GENERAL	HYPERTENSION AGGRAVATED	<1%
CARDIOVASCULAR- GENERAL	ANGINA PECTORIS	<1%
CARDIOVASCULAR- GENERAL	EDEMA DEPENDENT	<1%

Items in italics have been recoded from the Sponsor's initial preferred term to allow for combining related adverse events as described in the accompanying text.

Discussion of specific classes of adverse events follows:

Cardiac and Possible Cardiac events:

Acute myocardial infarctions occurred in 3 subjects: One never used Nicorette. One used 4mg gum for 2 months, and was not smoking. The MI occurred approximately 9 hours after the last Nicorette dose. The third subject to have an MI had used 4mg gum for 2 months and was still smoking.

Angina Pectoris was reported in 1 subject with a history of CHD. He had stopped using gum 1 month before.

Chest Pain was reported in 19 subjects. One subject with multiple medical problems had an episode of chest pain shortly after starting Nicorette but continued without incident until she had CHF and a pulmonary embolus 1 month after starting Nicorette. Twelve subjects had pain that was considered noncardiac in origin. The etiology of the pain in 6 subjects could not be determined. Eleven of these events occurred early in treatment and one subject stopped treatment.

Syncope was reported in 1 case of a person who used 2 pieces of 4mg gum at a time. Details of this subject's evaluation for syncope are not known but his physician recommended that he continue in the study.

Palpitations/Tachycardia were reported in 11 cases. In 2 of 3 persons with existing heart disease treatment with Nicorette was discontinued. In the third, the subject cut his dose back from 2 pieces of gum at a time every 2 hours and the symptoms resolved.

Among subjects with palpitations who did not have known heart disease: 1 subject had untreated hyperthyroidism; 3 subjects had episodes the first day and 1 subject stopped treatment at that time; 2 subjects had palpitations while continuing to smoke; 1 participant's symptoms resolved with dosage reduction from 7 pieces to 4 pieces of 4 mg gum/day).

Among 11 subjects with hypertension or aggravated hypertension, 6 had histories of hypertension, including 2 people who noted the problem in the first week and stopped the study. Other instances occurred 3 weeks to 3 months after starting Nicorette therapy.

It is difficult to attribute the observed myocardial infarctions in this study to Nicorette rather than to the long-term effects of smoking, (and possibly the stress of smoking cessation). The occurrence of chest pain early in treatment suggests a possible relationship to the study drug, but these events do not appear to represent emergence of serious unsuspected cardiac pathology. The occurrence of palpitations may be associated with pre-existing heart disease, may be associated with a lack of tolerance to Nicorette (oral nicotine) or may be a symptom of nicotine withdrawal, depending on the individual.

We think that the evidence for an unacceptable risk to these patients from inappropriate selection and/or use of the gum is very low.

GI events:

One incident of melena ("blood in stool") was reported in a patient receiving concomitant therapy with coumadin. The subject remained in the study.

Among 2 subjects reporting ulcers who were using Nicorette at the time, both had prior diagnoses of gastric or duodenal ulcer. One subject who was on ranitidine had resolution of symptoms when she cut her dose in half. The other subject attributed her symptoms to recent use of ketorolac.

In these patients, it is difficult to attribute the emergence of GI complaints to Nicorette exclusively, although it is possible that Nicorette may have played a contributory role. Subjects who reported histories of ulcers or heartburn had more complaints of nausea and dyspepsia than those who did not have this history.

Pregnancies:

One 19 year-old who had a positive pregnancy test was discontinued from the study after 2 weeks of treatment with 2mg Nicorette. She delivered a healthy baby. A 30 year old woman had delayed menses and may have had a miscarriage (she did not see her physician). She had been on 2mg Nicorette at the time. A 28 year-old woman on 2 mg gum noted in her diary that she became pregnant and miscarried during the first trimester. Both subjects who miscarried continued in the study, but failed to stop smoking.

Exploratory Analysis of Safety Data:

To examine the possible dose-relatedness of higher frequency adverse events, the prevalence of more common adverse events in this trial was examined by dose selected, by abstinence vs smoking at 6 weeks, and whether the subject purchased >4 boxes of gum in total regardless of dose). Incidence in the different patient groups for those events that occurred at least 5 times in each classification are given in the table below:

Incidence (%) of Common Adverse Events

Preferred Term	2 mg Gum N=1009	4 mg Gum N=1578	Abstinent Subjects N=432	Smoking Subjects N=2158	Purchased >4 Boxes N=534	Purchased <=4 Boxes N=2056
HEADACHE	19	16	27[P]	15	27[P]	15
NAUSEA	10	10	6[P]	10	6[P]	11
DYSPEPSIA	8	10	10	9	9	9
HICCUP	4[P]	10	10[P]	7	10[P]	6
THROAT IRRITATION	5	6	8	6	6	6
PSYCH	7[P]	5	9[P]	5	7	5
DIZZINESS	5	5	6	5	5	5
GASTRO-INTESTINAL	4	5	6	4	6	4
TOOTH DISORDER	5	4	7[P]	4	6[P]	4
STOMATITIS	3	4	4	4	4	4
FATIGUE	3	3	6[P]	3	5[P]	3
TASTE PERVERSION	3	3	2	3	1[P]	3
SINUSITIS	2	2	2	2	4[P]	1
JAWPAIN	2	2	3	2	4[P]	1
STOMATITIS APHTHOUS	2	2	3	2	3[P]	1
ABDOMINAL PAIN	2	2	3	1	2	2
CONSTIPATION	2	1	3[P]	1	2[P]	1
GINGIVITIS	1	1	2	1	2	1
GLOSSITIS	1	1	2	1	3[P]	1
DRY MOUTH	1	1	2[P]	1	2	1

[P]Significant difference between 2 mg and 4 mg, abstinent and smoking subjects, or >4 and <=4 boxes purchased ($p<0.05$, 2x2 chi square). p values only calculated for events having a frequency>5 in all cells.

Generally, the prevalence of adverse events was not affected by choice of dose strength. However, there is a clear tendency for dose-relatedness of adverse effects to emerge when adverse events are considered by subjects' smoking status at 6 weeks and by how many boxes of gum they purchased. Both of these measures should reflect greater overall gum use by participants. A notable exception to this is nausea, which occurred more frequently among subjects using less gum. This suggests that nausea may be a treatment limiting event or a withdrawal event.

Adverse Events during the first week of treatment:

Interpretation of the previous table may be clouded by the fact that long-term gum users had a longer period of exposure during which to develop adverse events. However, the same pattern of adverse events (consistent with higher prevalence of adverse events associated with long-term drug exposure) continues to be evident when one considers only the prevalence of adverse events during the first week of treatment:

Incidence (%) of Common Adverse Events (First Week of Treatment)

Preferred Term	2 mg Gum N=1009	4 mg Gum N=1578	Abstinent Subjects N=432	Smoking Subjects N=2158	Purchased >4 Boxes N=534	Purchased <=4 Boxes N=2056
HEADACHE	11	9	14	9	14.[P]	9
NAUSEA	8.0	8	5	8	4[P]	9
DYSPEPSIA	4.5	7	7	6	6	6
HICCUP	2.5	8	8	5	9[P]	5
THROAT IRRITATION	3.8	4	4	4	3	4
PSYCH	4.0	3	5	3	3	3
DIZZINESS	4.2	3	5	3	3	4
GASTRO-INTESTINAL	2.7	3	4	3	4	3
TOOTH DISORDER	1.7	1	1	2	1	2
STOMATITIS	1.9	3	2	3	2	3
FATIGUE	1.7	2	3	2	2	2
TASTE PERVERSION	1.8	2	1	3	1	3
SINUSITIS	<1	<1	1	<1	1	<1
JAWPAIN	1	1	1	1	2[P]	1
STOMATITIS APHTHOUS	1	1	1	1	1	1
ABDOMINAL PAIN	1	1	2	1	1	1
CONSTIPATION	1	1	2	1	1	1
GINGIVITIS	0	1	1	<1	1	<1
GLOSSITIS	<1	1.0	1	1	2[P]	<1
DRY MOUTH	1	<1	1	<1	1[P]	<1

[P]Significant difference between 2 mg and 4 mg, abstinent and smoking subjects, or >4 and <=4 boxes purchased ($p<0.05$, 2x2 chi square). p values only calculated for events having a frequency>5 in all cells.

Ethnicity, Gender, Age and Adverse Events:
Overall, 57% of subjects reported experiencing at least 1 adverse event (1464/2590). The crude adverse event rate among ethnic and gender subgroups is given in the table below:

Crude Adverse Event Rate:

Subgroup	Adverse Event Rate
All Subjects	**57%**
White Subjects	58%
Black Subjects	44%
Other Ethnicity	50%
Men	50%
Women	62%
Subjects>60	61%

Headache, nausea, and psychiatric complaints were more common among women than men. Hiccup, psychiatric complaints, tooth disorders, and stomatitis were approximately twice as common in subjects>60 than in younger subjects, when compared over the length of the entire study.

Labeling:
One of the primary objectives of this study was to test the ability of subjects to understand different aspects of labeling for OTC Nicorette. This included: 1] Making an appropriate decision to purchase Nicorette; and 2] Choosing the correct strength of gum to use. This was based on the subjects' understanding of the label they had read. The text of the warnings and precautions sections of the labeling as tested was:

WARNINGS: THIS PRODUCT IS ONLY FOR ADULTS 18 YEARS OR OLDER WHO WANT TO STOP SMOKING CIGARETTES. DO NOT SMOKE, CHEW TOBACCO OR USE SNUFF WHILE USING NICORETTE.

Smoking is dangerous, especially if you have heart disease including a recent heart attack, high blood pressure, diabetes, stomach ulcer, or if you are pregnant or breast feeding. The use of Nicorette by people with these conditions also has some risks. However, the risk is generally less than smoking, because Nicorette does not contain the harmful chemicals which are in cigarettes. If you smoke and have any of these conditions, ask your doctor to help you decide whether the benefits of quitting smoking with Nicorette out weigh the risks.

As with any drug, if you are pregnant or nursing a baby, seek the advice of a doctor before using this product.

Precaution: If you take prescription medication on a regular basis, consult your doctor before quitting smoking. Your dose may need to be adjusted. This is especially important if you are taking medicines for asthma or depression.

Assessment of intent to heed the labeled risk factors about seeing a doctor when using gum was complicated by the fact that only subjects who decided to purchase gum were specifically asked about the occurrence of labeled risk factors for which they should see a doctor before using gum, by the fact that many subjects had previously used nicotine replacement products and may therefore have reasonably considered that they had complied with the label recommendation regarding seeing a doctor before using this product, and the fact that the labeling tested compared the product to cigarettes, a health threat undoubtedly uppermost in the minds of potential Nicorette users.

It is difficult to determine the reasons for nonenrollment among 535 subjects screened who did not purchase Nicorette. Of these subjects 8% indicated that they had a risk factor for which they should see a doctor before using gum. Sixty percent of persons with a risk factor said that according to the label they would need to see a doctor before using the product although they may have also indicated additional reasons (e.g. cost) for not purchasing the product. The significance of this finding is unclear because the presence of labeled risk factors was unknown for 50%,

Among 1031 enrolled subjects who had previously purchased gum, 36% indicated that they had a labeled risk factor. Of these, 9% indicated that according to the label they needed to see a doctor

Overall, approximately 30% of the 2560 patients with evaluable responses indicated the presence of a labeled risk factor for which they should see a doctor before using gum, if they strictly followed the labeling. Of these 768 patients with a risk factor, 9% indicated that they would see a doctor before using Nicorette. The proportion of people purchasing gum who correctly understood whether they needed to see a doctor is as shown below:

Need To See A Doctor Based On Label (All Enrolled Subjects)

Patient's Response	Needed to See a Doctor (N=768)	No Need to See a Doctor (N=1792)
Patient Indicated a Need to See a Doctor	9%	4%
Patient Did Not Indicate a Need to See a Doctor	91%	96%

Subjects who did not respond to the question "do you need to see a doctor before using Nicorette?" are counted as answering "No".

Over 90% of patients who (according to the label) needed to see a doctor misperceived or ignored this advice. Some patients had had nicotine replacement products prescribed previously, so may have considered themselves as having seen a doctor. However, The same proportion (90%) of subjects who had not previously used nicotine replacement products failed to follow label warnings to see a doctor:

Patient who Needed To See A Doctor Based On Label (Enrolled Subjects With no Previous Gum or Patch Use)

Patient's Response	Needed to See a Doctor (N=395)	No Need to See a Doctor (N=2263)
Patient Indicated a Need to See a Doctor	10%	<1%
Patient Did Not Indicate a Need to See a Doctor	90%	99%

Subjects who did not respond to the question "do you need to see a doctor before using Nicorette?" are counted as answering "No".

Only a small fraction (approximately 10%) of the subjects who should seek medical advice based on the label would do so. This could indicate a problem

with the patients, the label, or both. This was examined and the results analyzed in the following section.

Exploratory Analysis of Intent to Heed Based on Medical Conditions Reported (Exploratory Analysis)

The possibility that the subjects' intent to heed the label warnings might be affected by the specificity of the warning was specifically considered. The breakdown of intent to heed the label warning to see a doctor by labeled risk factor is given in the table below:

Intent to Heed By Risk Factor (All Subjects Enrolled)

Risk Factor	Risk Factor Prevalence 2 mg Gum	Intent to Heed Label 2 mg gum	Risk Factor Prevalence 4 mg Gum	Intent to Heed Label 4 mg Gum
High BP	58(6%)	7(12%)	94(6%)	18(19%)
Recent M I	2(<1%)	0(0%)	2(<1%)	0(0%)
Ulcer	22(2%)	2(9%)	75(5%)	4(5%)
Diabetes	4(<1%)	2(50%)	11(1%)	3(27%)
Pregnancy	0(0%)	0(0%)	0(0%)	0(0%)
Breast Feeding	2(<1%)	0(0%)	0(0%)	0(0%)
Rx Medication	298(30%)	21(7%)	390(25%)	46(12%)
Depression/ Asthma	16(2%)	4(25%)	36(2%)	9(25%)
Any Risk Factor	319(32%)	22(14%)	447(29%)	49(11%)

Table made by the reviewer from the sponsor's electronic data set. Statistics for pregnancy and breast feeding are based on the number of women in the sample.

Regardless of the labeled conditions they reported, many subjects failed to heed the warnings, but the rate varies with the condition. This variation suggests that more specific description of conditions requiring medical advice may improve compliance with labeling.

The wording of the warnings and precautions statements tested was overly broad and lacked specificity (*any* prescription medication use). In addition, the warnings are described relative to cigarettes, a well-known and significant health threat the risks of which would already be uppermost in the minds of people purchasing this product and which would serve to minimize the impact of the warning on the reader *(its safer than smoking cigarettes)*. While this may be true, it may also have dissuaded many patients from seeking medical advice. We would recommend both making the exclusionary criteria more specific, and moderating the excessively reassuring language of the label.

Dose Selection:

Another of the principal objectives of this study was to determine the ability of subjects to decide which strength of gum was best for them. The cartons tested listed 4mg gum for those smoking over 25 cigarettes/day and 2mg gum for those smoking under 25 cigarettes/day. When the sponsor realized that the cartons did not provide instruction for people smoking exactly 25 cigarettes per day, the protocol was amended to include the use of tent-cards stating that the 4mg gum was intended for those smoking >= 25 cigarettes/day and that 2mg gum was for those smoking < 25 cigarettes/day.

Gum Recommended Based on Cigarettes Smoked

Gum Chosen	2mg recommended N=1144	4mg recommended N=1411
2mg	(76%)	(9%)
4mg	(24%)	(91%)

Table derived from the sponsor's electronic data set based on 2,555 subjects' who reported the number of cigarettes smoked at baseline as < 100/day.

While at least 90% of heavier smokers correctly selected the 4 mg gum, approximately 1/4 of lighter smokers incorrectly selected the 4 mg gum instead of the 2 mg gum. The error rates for gum choice are shown in the following table based on which label(s) were read:

Errors In Gum Selection By Label Read By Subject

Label Read By Subject	Chose 2mg Gum But "Should" Have Chosen 4mg Gum.	Chose 4mg Gum But "Should" Have Chosen 2mg Gum.
2mg Label	22/35(63%)	13/399(3%)
4mg Label	4/476(1%)	102/129(79%)
Both Labels	43/628(7%)	163/610(26%)

Table based on 2277 of 2286 subjects who indicated which label they read, smoked < 100 cigarettes/day and did not report smoking exactly 25 cigarettes/day at baseline.

These results suggest that: 1] subjects who read only one label were more likely to choose the box they read; 2] lighter smokers who read both labels were more likely to choose the incorrect gum strength than were heavier smokers who read both labels. This may have been an error on the part of the light smokers, or a decision on their part that they needed the higher strength.

In an effort to define the relationship between gum choice, baseline smoking behavior, abstinence, and adverse events, subjects were divided into 3 groups based on baseline CO, and Cigarettes/day at baseline.

	Baseline Exhaled CO		
Cigarettes/Day @Baseline	<21	>=21 and <31	>=31
<17	86% chose 2mg 14% chose 4mg N=313	80% chose 2mg 20% chose 4mg N=100	77% chose 2mg 23% chose 4mg N=57
Choice			
Abstinence	23% on 2mg 21% on 4mg	13% on 2mg 20% on 4mg	11% on 2mg 0% on 4mg
Any AE	57% on 2mg 48% on 4mg	55% on 2mg 60% on 4mg	70% on 2mg 31% on 4mg
>=17 and <31	51% chose 2mg 49% chose 4mg N=454	39% chose 2mg 61% chose 4mg N=471	31% chose 2mg 69% chose 4mg N=549
Choice			
Abstinence	23% on 2 mg 20% on 4 mg	15% on 2mg 15% on 4mg	10% on 2mg 17% on 4mg
Any AE	57% on 2mg 61% on 4mg	61% on 2mg 51% on 4mg	63% on 2mg 56% on 4mg
>=31	10% chose 2mg 90% chose 4mg N=106	2% chose 2mg 98% chose 4mg N=151	3% chose 2mg 97% chose 4mg N=350
Choice			
Abstinence	45% on 2mg 20% on 4mg	33% on 2mg 9% on 4mg	10% on 2mg 14% on 4mg
Any AE	36% on 2mg 63% on 4mg	33% on 2mg 48% on 4mg	70% on 2mg 57% on 4mg

Based on information available for 2551 of 2590 subjects. Subjects reporting smoking>=100 cigarettes/day had their levels of smoking set to int(baseline cigarettes per day /10). The cutoffs for the low and high smoking categories were set by those smoking less than the mean of the low dose group and the high dose group smoked >= the mean of the high dose group.

This analysis suggests that: 1. lightest smokers (low CO & low Cigarettes./day) tend to choose the 2mg gum, heavier smokers tend to chose the 4mg gum and those who smoke intermediate amounts are split in gum choice. 2. overall quit rates were higher in lighter smokers rather than heavier smokers and 3. erroneous gum choice appeared not be associated with a significantly increased incidence of adverse events.

Analysis of Gum Use:

Complete drug accountability data was available for 2540 of 2590 subjects in this trial. Gum purchases by subjects during the first 6 weeks of the trial were examined by dose group, smoking status at 6 weeks and by whether the subject purchased additional gum after the six week visit. Results of this analysis are presented in the table below:

Gum Use (Boxes Purchased) During First 6 Weeks By Dose, Smoking Status and Duration of Use

	2mg Gum	4mg Gum
Abstinent At 6 Weeks	3.0 (2.4) [183] 1-13	3.6 (2.2) [246] 1-15
Smoking At 6 Weeks	2.0 (1.9) [814] 1-17	2.1 (1.6) [1297] 0-16
Abstinent At 6 Weeks, Buying Additional Gum	4.1 (2.7) [90] 1-13	4.1 (2.2) [170] 1-15
Smoking At 6 Weeks, Buying Additional Gum	2.8 (2.3) [240] 1-16	2.7 (1.7) [419] 0-13

Mean (Standard Deviation) [N] Range

Boxes of Nicorette contained 96 pieces each. Therefore a purchase of 4 boxes would provide for a dose of 9 pieces/day for 6 weeks while 9 boxes would provide for an average dose of 20 pieces/day. A total of 33 subjects purchased enough gum in the first 6 weeks of the study (more than 9 boxes) to allow them to use more than 20 pieces/day and 19 subjects purchased enough gum (at least 18 boxes) during the entire 12 week period to allow them to use more than 20 pieces/day. The 5 subjects who reported feeling dependent on the gum purchased 1, 3, 5, 10, and 11 boxes.

A total of 1793 subjects completed the 12 week study visit. Of these, 973 (54%) reported that they had stopped using the gum by this time. Thirty-two percent of enrolled subjects reported they were continuing to use the gum at 12 weeks.

Conclusions

Abstinence in this study was 17% at 6 weeks. The data suggest that lighter smokers may be more likely to quit with Nicorette than more dependent smokers.

Adverse events observed in this trial were qualitatively similar to adverse events seen with prescriptive Nicorette (predominantly withdrawal type symptoms, GI symptoms, and oral/dental problems related to gum use.) Serious adverse events in this trial were either due to intercurrent illnesses, or events most likely to be the consequence of tobacco dependence, not medication usage.

Both light and heavy smokers were able to choose an appropriate dose of Nicorette. Erroneous dose selection was more common among lighter smokers who chose 4mg (heavier dose) gum. This choice may reflect inaccurately reported smoking. It may also be partly because labels tested only contained information about a single dosage strength. Whatever the cause, erroneous dose selection was not associated with a noticeable difference in adverse events.

In contrast to dose selection, this study had a low rate of intent-to-heed the label warnings about the need to see a doctor for labeled Nicorette risk factors. Although a low intent to heed is helpful in assessing the adverse event profile in a broader population, there is a need to revise the labeling to more accurately reflect the important risks to potential users.

To that end we would recommend the following principles:

Warnings should be as specific as possible.

Describing the product as 'safer' than smoking may lead people to ignore advice to see a doctor.

Many physicians involved with the trial did not consider the broadly worded warnings (e.g. any regular prescription drug use) to be contraindications to nicotine gum use. While some physicians may have considered the more specific warnings (e.g. serious cardiac disease) as potential reasons for caution in the use of Nicorette, this was not universal, with 16 of 39 sites enrolling a total of 1091 subjects accepting all persons desiring to participate.

Abuse and Dependence: 32% of subjects continued to use the gum for the entire 12 week study period. An additional 1-2% of subjects purchased enough gum to allow them to use more gum than recommended. Suitable warning should be placed in the label to alert patients to the possibility of dependence.

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SAFETY APPENDIX

TABLE 1: Absolute Numbers of All 4613 Adverse Events Among 1448 Subjects Who Experienced Only Nonserious Adverse Events (includes multiple occurrences per participant).

Sponsor's Preferred Term	Sponsor's Body System Classification	Total Number of Reports
HEADACHE	CENTR & PERIPH NERVOUS SYSTEM	759
NAUSEA	GASTRO-INTESTINAL SYSTEM	329
DYSPEPSIA	GASTRO-INTESTINAL SYSTEM	291
INFECTION VIRAL	RESISTANCE MECHANISM	285
HICCUP	GASTRO-INTESTINAL SYSTEM	240
ANXIETY	PSYCHIATRIC	199
THROAT IRRITATION	RESPIRATORY SYSTEM	172
NERVOUSNESS	PSYCHIATRIC	168
DIZZINESS	CENTR & PERIPH NERVOUS SYSTEM	149
TOOTH DISORDER	MOUTH/TOOTH DISORDERS	124
STOMATITIS	MOUTH/TOOTH DISORDERS	108
PAIN	BODY AS A WHOLE	106
FATIGUE	BODY AS A WHOLE	103
INSOMNIA	PSYCHIATRIC	96
TASTE PERVERSION	MOUTH/TOOTH DISORDERS	84
AGITATION	PSYCHIATRIC	83
STOMATITIS APHTHOUS	MOUTH/TOOTH DISORDERS	56
DEPRESSION	PSYCHIATRIC	56
COUGHING	RESPIRATORY SYSTEM	54
ABDOMINAL PAIN	GASTRO-INTESTINAL SYSTEM	54
CONSTIPATION	GASTRO-INTESTINAL SYSTEM	53
SINUSITIS	RESPIRATORY SYSTEM	51
CONGESTION	RESPIRATORY SYSTEM	49
BACK PAIN	MUSCULO-SKELETAL SYSTEM	49

Sponsor's Preferred Term	Sponsor's Body System Classification	Total Number of Reports
BRONCHITIS	RESPIRATORY SYSTEM	37
MEDICAL PROCEDURE	BODY AS A WHOLE	35
GINGIVITIS	MOUTH/TOOTH DISORDERS	35
VOMITING	GASTRO-INTESTINAL SYSTEM	32
GLOSSITIS	MOUTH/TOOTH DISORDERS	31
DRY MOUTH	AUTONOMIC NERVOUS SYSTEM	29
MIGRAINE HEADACHE	CENTR & PERIPH NERVOUS SYSTEM	28
ALLERGY	RESISTANCE MECHANISM	28
MALAISE	BODY AS A WHOLE	27
FLATULENCE	GASTRO-INTESTINAL SYSTEM	25
ARTHRALGIA	MUSCULO-SKELETAL SYSTEM	24
DIARRHEA	GASTRO-INTESTINAL SYSTEM	23
UPPER RESPIRATORY TRACT INFECTION	RESPIRATORY SYSTEM	22
MYALGIA	MUSCULO-SKELETAL SYSTEM	22
CHEST PAIN	CARDIOVASCULAR-GENERAL	22
ERUCTATION	GASTRO-INTESTINAL SYSTEM	21
INFLUENZA-LIKE SYMPTOMS	RESISTANCE MECHANISM	17
DYSMENORRHEA	REPRODUCTIVE- FEMALE	16
TONGUE ULCERATION	MOUTH/TOOTH DISORDERS	15
EARACHE	SPECIAL SENSES- OTHER	13
ARTHRITIS	MUSCULO-SKELETAL SYSTEM	13
URINARY TRACT INFECTION	RESISTANCE MECHANISM	12
SWEATING INCREASED	SKIN & APPENDAGES	12
TRAUMA INJURY	BODY AS A WHOLE	11
EAR DISORDER NOS	HEARING & VESTIBULAR	11
CONCENTRATION IMPAIRED	PSYCHIATRIC	11
RHINITIS	RESPIRATORY SYSTEM	10

Sponsor's Preferred Term	Sponsor's Body System Classification	Total Number of Reports
INFECTION	RESISTANCE MECHANISM	10
BONE DISORDER	MUSCULO-SKELETAL SYSTEM	10
HYPERTENSION	CARDIOVASCULAR-GENERAL	9
FEVER	BODY AS A WHOLE	9
BRONCHOSPASM	RESPIRATORY SYSTEM	9
PALPITATION	HEART RATE & RHYTHM	8
TACHYCARDIA	HEART RATE & RHYTHM	6
HOT FLUSHES	VASCULAR (EXTRACARDIAC)	6
DYSPNEA	RESPIRATORY SYSTEM	6
ASTHENIA	BODY AS A WHOLE	6
ANOREXIA	GASTRO-INTESTINAL SYSTEM	6
ADVERSE REACTION ILL DEFINED	BODY AS A WHOLE	6
VAGINITIS	REPRODUCTIVE- FEMALE	5
THIRST	GASTRO-INTESTINAL SYSTEM	5
SNEEZING	RESPIRATORY SYSTEM	5
RASH	SKIN & APPENDAGES	5
DRUG DEPENDENCE	PSYCHIATRIC	5
CONFUSION	PSYCHIATRIC	5
TENDINITIS	MUSCULO-SKELETAL SYSTEM	4
RHINORRHEA	RESPIRATORY SYSTEM	4
PREMENSTRUAL SYMPTOMS	REPRODUCTIVE- FEMALE	4
PNEUMONIA	RESPIRATORY SYSTEM	4
NIGHTMARE	PSYCHIATRIC	4
LARYNGITIS	RESPIRATORY SYSTEM	4
HERPES SIMPLEX	SKIN & APPENDAGES	4
GASTROENTERITIS	GASTRO-INTESTINAL SYSTEM	4
EPISTAXIS	RESPIRATORY SYSTEM	4
VISION ABNORMAL	VISION	3
TREMOR	CENTR & PERIPH NERVOUS SYSTEM	3

Sponsor's Preferred Term	Sponsor's Body System Classification	Total Number of Reports
SALIVA INCREASED	MOUTH/TOOTH DISORDERS	3
MENSTRUAL DISORDER	REPRODUCTIVE- FEMALE	3
LACRIMATION ABNORMAL	VISION	3
BRONCHOSPASM AGGRAVATED	RESPIRATORY SYSTEM	3
ATAXIA	CENTR & PERIPH NERVOUS SYSTEM	3
ACNE	SKIN & APPENDAGES	3
ULCER- UNSPECIFIED	GASTRO-INTESTINAL SYSTEM	2
TOOTH CARIES	MOUTH/TOOTH DISORDERS	2
TASTE LOSS	MOUTH/TOOTH DISORDERS	2
RENAL CALCULUS	URINARY SYSTEM	2
PRURITUS	SKIN & APPENDAGES	2
PREGNANCY UNINTENDED	REPRODUCTIVE- FEMALE	2
PHLEBITIS	VASCULAR (EXTRACARDIAC)	2
PARESTHESIA	CENTR & PERIPH NERVOUS SYSTEM	2
NASAL IRRITATION	RESPIRATORY SYSTEM	2
NAIL DISORDER	SKIN & APPENDAGES	2
MYOPATHY	MUSCULO-SKELETAL SYSTEM	2
LYMPHADENOPATHY	RESISTANCE MECHANISM	2
INFECTION FUNGAL	RESISTANCE MECHANISM	2
HYPERTONIA	MUSCULO-SKELETAL SYSTEM	2
HYPERTENSION AGGRAVATED	CARDIOVASCULAR-GENERAL	2
HYPERCHOLESTEROLEMIA	METABOLIC & NUTRITIONAL	2
HERPES ZOSTER	SKIN & APPENDAGES	2
GINGIVAL BLEEDING	MOUTH/TOOTH DISORDERS	2
GASTROESOPHAGEAL REFLUX	GASTRO-INTESTINAL SYSTEM	2
GASTRO-INTESTINAL DISORDER NOS	GASTRO-INTESTINAL SYSTEM	2
GASTRITIS	GASTRO-INTESTINAL SYSTEM	2

Sponsor's Preferred Term	Sponsor's Body System Classification	Total Number of Reports
FLUSHING	VASCULAR (EXTRACARDIAC)	2
EYE ABNORMALITY	VISION	2
EMOTIONAL LABILITY	PSYCHIATRIC	2
DROWSINESS	CENTR & PERIPH NERVOUS SYSTEM	2
DREAMING ABNORMAL	PSYCHIATRIC	2
DIVERTICULITIS	GASTRO-INTESTINAL SYSTEM	2
DEPERSONALIZATION	PSYCHIATRIC	2
DEATH FETAL	FETAL DISORDERS	2
CRAMPS LEGS	MUSCULO-SKELETAL SYSTEM	2
COUGH NONPRODUCTIVE	RESPIRATORY SYSTEM	2
CONJUNCTIVITIS	VISION	2
COLITIS	GASTRO-INTESTINAL SYSTEM	2
CENTRAL NERVOUS SYSTEM DISORDER NOS	CENTR & PERIPH NERVOUS SYSTEM	2
ARTHROSIS	MUSCULO-SKELETAL SYSTEM	2
APATHY	BODY AS A WHOLE	2
AMNESIA	PSYCHIATRIC	2
ALLERGIC REACTION	RESISTANCE MECHANISM	2
WHEEZING	RESPIRATORY SYSTEM	1
WEIGHT DECREASE	BODY AS A WHOLE	1
VAGINAL HEMORRHAGE	REPRODUCTIVE- FEMALE	1
UTERINE HEMORRHAGE	REPRODUCTIVE- FEMALE	1
URTICARIA	SKIN & APPENDAGES	1
URINE ABNORMAL	URINARY SYSTEM	1
URINATION DISORDER	URINARY SYSTEM	1
URINARY FREQUENCY	URINARY SYSTEM	1
TONGUE EDEMA	MOUTH/TOOTH DISORDERS	1
TONGUE DISCOLORATION	MOUTH/TOOTH DISORDERS	1
THYROIDITIS	ENDOCRINE	1
THYROID DISORDER	ENDOCRINE	1
SYNCOPE	CENTR & PERIPH NERVOUS	1

Sponsor's Preferred Term	Sponsor's Body System Classification	Total Number of Reports
	SYSTEM	
SPUTUM INCREASED	RESPIRATORY SYSTEM	1
SPASM GENERALIZED	CENTR & PERIPH NERVOUS SYSTEM	1
SLEEP DISORDER	PSYCHIATRIC	1
RIGORS	BODY AS A WHOLE	1
RESPIRATORY DISORDER	RESPIRATORY SYSTEM	1
RASH PSORIAFORM	SKIN & APPENDAGES	1
PNEUMONIA LOBAR	RESPIRATORY SYSTEM	1
PEPTIC ULCER	GASTRO-INTESTINAL SYSTEM	1
PAROSMIA	SPECIAL SENSES- OTHER	1
OLIGURIA	URINARY SYSTEM	1
NO ADVERSE REACTION	OTHER	1
NEUROSIS	PSYCHIATRIC	1
MUSCULOSKELETAL DISORDER	MUSCULO-SKELETAL SYSTEM	1
MUCUS MEMBRANE DISORDER	BODY AS A WHOLE	1
MELENA	GASTRO-INTESTINAL SYSTEM	1
INFECTION BACTERIAL	RESISTANCE MECHANISM	1
HYPOTHYROIDISM	ENDOCRINE	1
HYPOKALEMIA	METABOLIC & NUTRITIONAL	1
HYPOESTHESIA	CENTR & PERIPH NERVOUS SYSTEM	1
HYPERTHYROIDISM	ENDOCRINE	1
HYPERLIPEMIA	METABOLIC & NUTRITIONAL	1
HERNIA	MUSCULO-SKELETAL SYSTEM	1
HALITOSIS	MOUTH/TOOTH DISORDERS	1
GAIT ABNORMAL	CENTR & PERIPH NERVOUS SYSTEM	1
FURUNCULOSIS	SKIN & APPENDAGES	1
FOLATE SERUM TEST ABNORMAL	METABOLIC & NUTRITIONAL	1
ERYTHEMA	SKIN & APPENDAGES	1
EDEMA GENERALIZED	BODY AS A WHOLE	1
EDEMA DEPENDENT	CARDIOVASCULAR-	1

Sponsor's Preferred Term	Sponsor's Body System Classification	Total Number of Reports
	GENERAL	
ECZEMA	SKIN & APPENDAGES	1
DYSPHONIA	SPECIAL SENSES- OTHER	1
DYSPHAGIA	GASTRO-INTESTINAL SYSTEM	1
DIABETES MELLITUS	METABOLIC & NUTRITIONAL	1
DERMATITIS	SKIN & APPENDAGES	1
DEHYDRATION	BODY AS A WHOLE	1
COORDINATION ABNORMAL	CENTR & PERIPH NERVOUS SYSTEM	1
CERVICAL DYSPLASIA	REPRODUCTIVE- FEMALE	1
CANDIDIASIS	RESISTANCE MECHANISM	1
BLADDER CALCULUS	URINARY SYSTEM	1
ATHEROSCLEROSIS	VASCULAR (EXTRACARDIAC)	1
ANGINA PECTORIS	CARDIOVASCULAR-GENERAL	1
ABDOMINAL DISTENSION	GASTRO-INTESTINAL SYSTEM	1

TABLE 2: Absolute Numbers of Unique Occurances of 3305 non-withdrawal Adverse Events Among 1410 Subjects Who Experienced Only Nonserious Adverse Events.

Sponsor's Preferred Term	Sponsor's Body System Classification	Total Number of Events
HEADACHE	CENTR & PERIPH NERVOUS SYSTEM	444
NAUSEA	GASTRO-INTESTINAL SYSTEM	251
INFECTION VIRAL	RESISTANCE MECHANISM	240
DYSPEPSIA	GASTRO-INTESTINAL SYSTEM	230
HICCUP	GASTRO-INTESTINAL SYSTEM	185
THROAT IRRITATION	RESPIRATORY SYSTEM	151
DIZZINESS	CENTR & PERIPH NERVOUS SYSTEM	127
TOOTH DISORDER	MOUTH/TOOTH DISORDERS	107
STOMATITIS	MOUTH/TOOTH DISORDERS	98
PAIN	BODY AS A WHOLE	87
FATIGUE	BODY AS A WHOLE	80
TASTE PERVERSION	MOUTH/TOOTH DISORDERS	76
INSOMNIA	PSYCHIATRIC	66
SINUSITIS	RESPIRATORY SYSTEM	51
DEPRESSION	PSYCHIATRIC	50
COUGHING	RESPIRATORY SYSTEM	50
STOMATITIS APHTHOUS	MOUTH/TOOTH DISORDERS	45
CONGESTION	RESPIRATORY SYSTEM	43
ABDOMINAL PAIN	GASTRO-INTESTINAL SYSTEM	42
BRONCHITIS	RESPIRATORY SYSTEM	37
BACK PAIN	MUSCULO-SKELETAL SYSTEM	37
MEDICAL PROCEDURE	BODY AS A WHOLE	34
CONSTIPATION	GASTRO-INTESTINAL SYSTEM	32
GINGIVITIS	MOUTH/TOOTH DISORDERS	29
VOMITING	GASTRO-INTESTINAL SYSTEM	26
GLOSSITIS	MOUTH/TOOTH DISORDERS	26

Sponsor's Preferred Term	Sponsor's Body System Classification	Total Number of Events
ALLERGY	RESISTANCE MECHANISM	26
MALAISE	BODY AS A WHOLE	25
DIARRHEA	GASTRO-INTESTINAL SYSTEM	22
DRY MOUTH	AUTONOMIC NERVOUS SYSTEM	21
ARTHRALGIA	MUSCULO-SKELETAL SYSTEM	21
FLATULENCE	GASTRO-INTESTINAL SYSTEM	20
ERUCTATION	GASTRO-INTESTINAL SYSTEM	20
UPPER RESPIRATORY TRACT INFECTION	RESPIRATORY SYSTEM	19
MYALGIA	MUSCULO-SKELETAL SYSTEM	18
CHEST PAIN	CARDIOVASCULAR-GENERAL	18
INFLUENZA-LIKE SYMPTOMS	RESISTANCE MECHANISM	17
MIGRAINE HEADACHE	CENTR & PERIPH NERVOUS SYSTEM	16
DYSMENORRHEA	REPRODUCTIVE- FEMALE	14
TONGUE ULCERATION	MOUTH/TOOTH DISORDERS	13
URINARY TRACT INFECTION	RESISTANCE MECHANISM	12
EARACHE	SPECIAL SENSES- OTHER	12
TRAUMA INJURY	BODY AS A WHOLE	11
SWEATING INCREASED	SKIN & APPENDAGES	11
EAR DISORDER NOS	HEARING & VESTIBULAR	11
ARTHRITIS	MUSCULO-SKELETAL SYSTEM	11
RHINITIS	RESPIRATORY SYSTEM	10
INFECTION	RESISTANCE MECHANISM	10
BONE DISORDER	MUSCULO-SKELETAL SYSTEM	10
HYPERTENSION	CARDIOVASCULAR-GENERAL	9
FEVER	BODY AS A WHOLE	9
BRONCHOSPASM	RESPIRATORY SYSTEM	9

Sponsor's Preferred Term	Sponsor's Body System Classification	Total Number of Events
TACHYCARDIA	HEART RATE & RHYTHM	6
HOT FLUSHES	VASCULAR (EXTRACARDIAC)	6
ASTHENIA	BODY AS A WHOLE	6
ANOREXIA	GASTRO-INTESTINAL SYSTEM	6
ADVERSE REACTION ILL DEFINED	BODY AS A WHOLE	6
VAGINITIS	REPRODUCTIVE- FEMALE	5
THIRST	GASTRO-INTESTINAL SYSTEM	5
SNEEZING	RESPIRATORY SYSTEM	5
RASH	SKIN & APPENDAGES	5
PALPITATION	HEART RATE & RHYTHM	5
DYSPNEA	RESPIRATORY SYSTEM	5
DRUG DEPENDENCE	PSYCHIATRIC	5
TENDINITIS	MUSCULO-SKELETAL SYSTEM	4
RHINORRHEA	RESPIRATORY SYSTEM	4
PREMENSTRUAL SYMPTOMS	REPRODUCTIVE- FEMALE	4
PNEUMONIA	RESPIRATORY SYSTEM	4
NIGHTMARE	PSYCHIATRIC	4
NERVOUSNESS	PSYCHIATRIC	4
LARYNGITIS	RESPIRATORY SYSTEM	4
HERPES SIMPLEX	SKIN & APPENDAGES	4
GASTROENTERITIS	GASTRO-INTESTINAL SYSTEM	4
EPISTAXIS	RESPIRATORY SYSTEM	4
ANXIETY	PSYCHIATRIC	4
VISION ABNORMAL	VISION	3
TREMOR	CENTR & PERIPH NERVOUS SYSTEM	3
SALIVA INCREASED	MOUTH/TOOTH DISORDERS	3
MENSTRUAL DISORDER	REPRODUCTIVE- FEMALE	3
CONFUSION	PSYCHIATRIC	3
BRONCHOSPASM AGGRAVATED	RESPIRATORY SYSTEM	3
AGITATION	PSYCHIATRIC	3
ACNE	SKIN & APPENDAGES	3

Sponsor's Preferred Term	Sponsor's Body System Classification	Total Number of Events
ULCER- UNSPECIFIED	GASTRO-INTESTINAL SYSTEM	2
TOOTH CARIES	MOUTH/TOOTH DISORDERS	2
TASTE LOSS	MOUTH/TOOTH DISORDERS	2
RENAL CALCULUS	URINARY SYSTEM	2
PRURITUS	SKIN & APPENDAGES	2
PREGNANCY UNINTENDED	REPRODUCTIVE- FEMALE	2
PHLEBITIS	VASCULAR (EXTRACARDIAC)	2
PARESTHESIA	CENTR & PERIPH NERVOUS SYSTEM	2
NASAL IRRITATION	RESPIRATORY SYSTEM	2
NAIL DISORDER	SKIN & APPENDAGES	2
MYOPATHY	MUSCULO-SKELETAL SYSTEM	2
LYMPHADENOPATHY	RESISTANCE MECHANISM	2
LACRIMATION ABNORMAL	VISION	2
INFECTION FUNGAL	RESISTANCE MECHANISM	2
HYPERTONIA	MUSCULO-SKELETAL SYSTEM	2
HYPERTENSION AGGRAVATED	CARDIOVASCULAR-GENERAL	2
HYPERCHOLESTEROLEMIA	METABOLIC & NUTRITIONAL	2
HERPES ZOSTER	SKIN & APPENDAGES	2
GINGIVAL BLEEDING	MOUTH/TOOTH DISORDERS	2
GASTROESOPHAGEAL REFLUX	GASTRO-INTESTINAL SYSTEM	2
GASTRO-INTESTINAL DISORDER NOS	GASTRO-INTESTINAL SYSTEM	2
GASTRITIS	GASTRO-INTESTINAL SYSTEM	2
FLUSHING	VASCULAR (EXTRACARDIAC)	2
EYE ABNORMALITY	VISION	2
EMOTIONAL LABILITY	PSYCHIATRIC	2
DROWSINESS	CENTR & PERIPH NERVOUS SYSTEM	2
DREAMING ABNORMAL	PSYCHIATRIC	2

Sponsor's Preferred Term	Sponsor's Body System Classification	Total Number of Events
DIVERTICULITIS	GASTRO-INTESTINAL SYSTEM	2
DEPERSONALIZATION	PSYCHIATRIC	2
DEATH FETAL	FETAL DISORDERS	2
CRAMPS LEGS	MUSCULO-SKELETAL SYSTEM	2
COUGH NONPRODUCTIVE	RESPIRATORY SYSTEM	2
CONJUNCTIVITIS	VISION	2
COLITIS	GASTRO-INTESTINAL SYSTEM	2
CENTRAL NERVOUS SYSTEM DISORDER NOS	CENTR & PERIPH NERVOUS SYSTEM	2
ATAXIA	CENTR & PERIPH NERVOUS SYSTEM	2
ARTHROSIS	MUSCULO-SKELETAL SYSTEM	2
ALLERGIC REACTION	RESISTANCE MECHANISM	2
WHEEZING	RESPIRATORY SYSTEM	1
WEIGHT DECREASE	BODY AS A WHOLE	1
VAGINAL HEMORRHAGE	REPRODUCTIVE- FEMALE	1
UTERINE HEMORRHAGE	REPRODUCTIVE- FEMALE	1
URTICARIA	SKIN & APPENDAGES	1
URINE ABNORMAL	URINARY SYSTEM	1
URINATION DISORDER	URINARY SYSTEM	1
URINARY FREQUENCY	URINARY SYSTEM	1
TONGUE EDEMA	MOUTH/TOOTH DISORDERS	1
TONGUE DISCOLORATION	MOUTH/TOOTH DISORDERS	1
THYROIDITIS	ENDOCRINE	1
THYROID DISORDER	ENDOCRINE	1
SYNCOPE	CENTR & PERIPH NERVOUS SYSTEM	1
SPUTUM INCREASED	RESPIRATORY SYSTEM	1
SPASM GENERALIZED	CENTR & PERIPH NERVOUS SYSTEM	1
SLEEP DISORDER	PSYCHIATRIC	1
RIGORS	BODY AS A WHOLE	1
RESPIRATORY DISORDER	RESPIRATORY SYSTEM	1

Sponsor's Preferred Term	Sponsor's Body System Classification	Total Number of Events
RASH PSORIAFORM	SKIN & APPENDAGES	1
PNEUMONIA LOBAR	RESPIRATORY SYSTEM	1
PEPTIC ULCER	GASTRO-INTESTINAL SYSTEM	1
PAROSMIA	SPECIAL SENSES- OTHER	1
OLIGURIA	URINARY SYSTEM	1
NO ADVERSE REACTION	OTHER	1
MUSCULOSKELETAL DISORDER	MUSCULO-SKELETAL SYSTEM	1
MUCUS MEMBRANE DISORDER	BODY AS A WHOLE	1
MELENA	GASTRO-INTESTINAL SYSTEM	1
INFECTION BACTERIAL	RESISTANCE MECHANISM	1
HYPOTHYROIDISM	ENDOCRINE	1
HYPOKALEMIA	METABOLIC & NUTRITIONAL	1
HYPOESTHESIA	CENTR & PERIPH NERVOUS SYSTEM	1
HYPERTHYROIDISM	ENDOCRINE	1
HYPERLIPEMIA	METABOLIC & NUTRITIONAL	1
HERNIA	MUSCULO-SKELETAL SYSTEM	1
HALITOSIS	MOUTH/TOOTH DISORDERS	1
GAIT ABNORMAL	CENTR & PERIPH NERVOUS SYSTEM	1
FURUNCULOSIS	SKIN & APPENDAGES	1
FOLATE SERUM TEST ABNORMAL	METABOLIC & NUTRITIONAL	1
ERYTHEMA	SKIN & APPENDAGES	1
EDEMA GENERALIZED	BODY AS A WHOLE	1
EDEMA DEPENDENT	CARDIOVASCULAR-GENERAL	1
ECZEMA	SKIN & APPENDAGES	1
DYSPHONIA	SPECIAL SENSES- OTHER	1
DYSPHAGIA	GASTRO-INTESTINAL SYSTEM	1
DIABETES MELLITUS	METABOLIC & NUTRITIONAL	1
DERMATITIS	SKIN & APPENDAGES	1
DEHYDRATION	BODY AS A WHOLE	1

Sponsor's Preferred Term	Sponsor's Body System Classification	Total Number of Events
COORDINATION ABNORMAL	CENTR & PERIPH NERVOUS SYSTEM	1
CERVICAL DYSPLASIA	REPRODUCTIVE- FEMALE	1
CANDIDIASIS	RESISTANCE MECHANISM	1
BLADDER CALCULUS	URINARY SYSTEM	1
ATHEROSCLEROSIS	VASCULAR (EXTRACARDIAC)	1
APATHY	BODY AS A WHOLE	1
ANGINA PECTORIS	CARDIOVASCULAR-GENERAL	1
AMNESIA	PSYCHIATRIC	1
ABDOMINAL DISTENSION	GASTRO-INTESTINAL SYSTEM	1
		1
NEUROSIS	PSYCHIATRIC	0
CONCENTRATION IMPAIRED	PSYCHIATRIC	0