CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-612/S025

20-066/S007

MEDICAL REVIEW

DEC 17 1998

Division of Over-the-Counter Drug Products
Medical Officer Review

Applicant:	SmithKline Beecham
NDA No:	18-612/S-025
	20-066/S-007 ✓
Product:	Nicorette gum (Mint Flavor) 2 mg
	Nicorette gum (Mint Flavor) 4 mg
Submission:	NDA Supplement dated May 15, 1998
	Additional Information dated September 28, 1998
Date Reviewed:	August 1998
Date Completed:	December 1998

Introduction

SmithKline Beecham filed a supplement for the addition of mint flavoring to their existing NDAs for Nicorette gum 2 and 4 mg. Nicorette gum was approved as a prescription (Rx) product in 1992. The gum was switched to Over-the-Counter (OTC) status and launched in the U.S. marketplace in April 1996. Mint Nicorette has never been marketed in the U.S., either as a prescription or OTC product. Thus, postmarketing experience of the Nicorette gum in other countries (original and flavored) and in the U.S. (original flavor) will be examined in this review.

Marketing

A. Worldwide

Mint Nicorette is currently registered in 35 countries worldwide. It has Rx status in 5 countries and OTC status in the other 30 countries. The product has not been launched in 7 countries. (Subsequent information from the sponsor revealed that Nicorette was launched this fall in Rumania and Hong Kong, and will be launched in Greece in 1999. In the 4 other countries where the product is still not launched, the reasons are mainly due to the lack of a marketing organization and/or low demand for the product.) Table 1 lists the countries where Mint Nicorette 2 mg and 4 mg is currently available. The sponsor stated that Mint Nicorette has not been withdrawn from any foreign market where it has been introduced.

Table 1: Foreign Market Status of Mint Nicorette Gum 2 mg & 4 mg

Country	Registration	Launch 2 mg and 4 mg	Status
Canada	1991	4/91	OTC/PO
Germany	1991	1/94	OTC/PO
Sweden	1992	3/92	OTC/PO
Switzerland	1992	10/92	OTC/PO
Norway	1992	10/92	OTC/PO
Colombia	1992	3/93	OTC/PO
Iceland	1993	?/93	OTC/PO
Poland	1993	10/93	OTC/PO
England	1993	9/93	OTC/PO
Aruba	1993	Not launched	Rx
Denmark	1993	?/93	OTC/PO
Finland	1993	12/93	OTC/PO
Ireland	1993	12/93	OTC/PO
Mexico	1993	Q1/94	OTC/PO
Australia	1993	5/94	OTC/PO
Netherlands	1993	Not launched	Rx
New Zealand	1993	5/93	OTC/PO
Croatia	1993	?/95	Rx
Spain	1993	3/96*	OTC/PO
Cyprus	1994	?	OTC/PO
Austria	1994	11/94	OTC/PO
Estonia	1994	7/94	OTC/PO
Lithuania	1994	Q2/95	OTC/PO
Holland	1995	5/95	OTC/PO
Italy	1995	10/95	OTC/PO
Czech Rep	1995	7/97	OTC/PO
Belgium	1995	1/96	OTC/PO
Latvia	1995	Q1/95	OTC/PO
Luxembourg	1996	?/96	OTC/PO
Hungary	1996	Not launched	OTC/PO
Rumania	1997	Not launched	OTC/PO
France	1997	4/97*	OTC/PO
Greece	1997	Not launched	Rx
Bulgaria	1997	Not launched	OTC/PO
Hong Kong	1997	Not launched	Rx

PO: Pharmacy Only; dispensed under pharmacist's supervision
* 4 mg Mint Nicorette is still Rx in Spain and France

Sales information was provided for the countries listed in Table 2 below. In the U.K., sponsor reported that Mint Nicorette gum represented 25% of total Nicorette units sold by 1997. In Sweden, Mint Nicorette gum represented 24% of total Nicorette units sold in 1997.

Table 2: Mint Nicorette gum Sales 1990 to 1998 (in millions of boxes sold)

Country	# Boxes Sold 2 mg	Time Period	# Boxes Sold 4mg	Time Period
UK	[redacted]	Q3/93 – Q2/98	[redacted]	Q3/93 – Q2/98
Sweden	[redacted]	Q2/92 – Q1/98	[redacted]	Q2/92 – Q1/98
Spain	[redacted]	Q1/96 – Q2/98	[redacted]	
Italy	[redacted]		[redacted]	Q4/95 – Q2/98
France	[redacted]	Q2/97 – Q2/98	[redacted]	
Germany	[redacted]	Q1/92 – Q2/98	[redacted]	Q1/92 – Q2/98

Medical Officer's Comments:

While Mint Nicorette gum has not been marketed in the U.S., there is substantial OTC marketing of the same product in other countries worldwide. For the countries where sales data was provided (in some countries as far back as 1992), approximately ——— boxes of Mint Nicorette gum have been sold, of which ——— boxes were for the 4 mg strength gum.

B. U.S.

As stated previously, in the U.S., Mint Nicorette gum is only available in the original flavor. As of July of 1998, a total of ——— boxes have been sold, of which ——— boxes are in the 4 mg strength. Of the total number of boxes sold, 57.5% were for the refill pack, which contains 48 pieces, while the others are for the 2-week supply pack, which has 108 pieces of gum.

Postmarketing Safety Experience

The report on worldwide adverse events did not make a distinction between original flavor and other flavors of gum, nor between the 2 mg and 4 mg gum specifically. Unless otherwise stated, it is assumed that the reports involve all flavors and strengths of Nicorette. Adverse events reported in the U.S. are for the original flavor Nicorette only.

A. Deaths

A total of 5 fatal cases were reported in the September 28, 1998 submission. See Table 5 below for a summary of these cases.

Table 3: Summary of Deaths

ID Number	Place	Date	Age	Sex	Event	Medical History	Comment
1994012346	UK	11/94	?	M	Died 12 days post hospital discharge	Literature report; entered into post-MI study on Nicorette 2 mg	S/P MI, 12 days post hospital discharge, +PVCs
1995012027	Japan	11/95	67	M	10/30/95: chest pain after dinner party with alcohol and cigarettes. Cardiac arrest en route to hospital	Smoker since age 20 50 cigs daily from age 40 Daily alcohol use Mild emphysema Advised to quit smoking Used 2 mg gum 9/20/95 to 10/29/95. In 10/95. smoked 10 cigs/day and used 2-3 pieces of 2 mg gum/day	Coroner suspected MI
1998004083	Japan	1/98	37	M	1/16/98: found dead while sleeping	Smoker; 40 cigs/day Obesity, Hyperlipidemia, on fenofibrate & another hyperlipidemia drug Had normal treadmill & holter monitoring 12/17/97 to 1/14/98: calculated total of 20 pieces for 28 days	MI suspected; autopsy not done
1997024971	US	1/98	44	M	9/18/97: found pulseless in car by EMT; in v-fib Wife reported chest pain in AM	Smoker 1 ppd X 20 yrs Smoked ½ ppd while on Nicorette 4 mg	Cardiac arrest
1996007325	US	3/97	69	F	1/2/97: died	'90: lobectomy for lung ca H/o smoking Used Nicorette X 15 yrs S/P stroke	Unknown cause

Medical Officer's Comments:

Of the 5 fatal cases, 4 probably died from cardiac related causes. A probable cause of death in the 69 y.o. female in the US was not specified. In the remaining 4 deaths, a cardiac etiology was suspect. Certainly the 2 cases in Japan had significant smoking histories and both continued smoking while using Nicorette, although the amount of Nicorette used did not appear excessive. The case in the US also continued to smoke while using Nicorette, however there is no information on whether he had pre-existing cardiac disease. The case in the U.K. occurred in a subject who just had an MI. While a definitive conclusion that these deaths are drug related cannot be made on the basis of the information available, the time-relatedness of the event to drug use (i.e. still using or within days of the event) should be noted.

The safety with the use of Nicorette in persons with high risk of cardiac compromise had been raised at the time of the initial switch of the nicotine replacement therapies (NRT). The current labeling does address underlying cardiac conditions in the Warning:

"**Ask your doctor before use if you:**

- have heart disease, recent heart attack, or irregular heartbeat
- have high blood pressure not controlled with medication
- have stomach ulcer or take insulin for diabetes
- take prescription medicine for depression or asthma."

The number of cases reported is within the range expected for the general population and certainly for a population of smokers. However, the issue of risk with the continued use of Nicorette gum (or other NRTs) remains an issue of continued debate.

B. 15-Day Reports

The sponsor in their listing of the 15-Day Reports included the 5 fatal cases described above. These 5 cases will be excluded from Tables 4 and 5, as they have already been discussed.

Table 4: List of 15-Day Reports: Nicorette 2 mg

Number	Date	Event
96004474	4/96	60 y.o. female with diagnosis of cancer of the tongue. Used Nicorette for 7 years. Patient had history of heavy smoking (quit 5 yrs ago) and heavy alcohol use
96008537	6/96	Anaphylactic reaction with IV infusion of Zofran & Hexadrol for chemotherapy pretreatment. Treated in ER with resolution.
96008883	6/96	Used Nicorette for 4 years ('90-'94). Stopped when cancerous tumor removed from tongue. Resumed smoking. Restarted Nicorette9/95 till present; 20 pieces/d. Has receding gums.
96010390	7/96	Headache with first use of ½ piece of gum. Migraine after three ½ pieces with nausea & dry heaves. Treated in ER with resolution. H/o migraine.
96011918	9/96	S/P mastectomy 6/95. Used Nicorette, up to 10-12 pieces/day for 4 years. Stated she is addicted to product; has tried to wean several times.
96017881	11/96	48 y.o. female experienced severe depression one morning after chewing 1 piece of gum daily since 9/95. Suicide attempt later that day. Called paramedics and admitted. Discharged with diagnosis of schizophrenia. Meds since '94: Carbamazepine, Thiothixene, Hydroxyzine.
96013477	1/97 5/97	Asthmatic allergic reaction. Patient has h/o asthma, on medication. Treated in ER and admitted with resolution.
97007306	3/97	Swelling of tongue 2 days after starting Nicorette. Admitted to hospital. Resolution with discontinuation of drug.
1997031126 (France)	3/98	Started Nicorette 8/96. Also started intensive sports; experienced tachycardia. Work up revealed coronary stenosis; surgery performed.

Table 5: List of 15-Day Reports: Nicorette 4 mg

Number	Date	Event
96008014	7/96 8/96 9/96 4/97 5/97	Consumer c/o right arm pain, with numbness & tingling, then loss of use of right hand, with use of Nicorette, 4-5 pieces/d. ER diagnosis was nerve entrapment vs. Mononeuropathy. Other hospital records had ? for etiology. Further workup 3/97: C3-C4 disc herniation, normal EMG in upper extremity, abnormal NCV in upper extremity. Symptoms improved on Elavil. Multiple medical histories including COPD, asbestos exposure, asthma, anxiety, arthritis, sarcoidosis, neuropathy, diabetes.
96007745	7/96	Prolonged difficulty breathing for several weeks; bluish fingertips and toes, and peripheral edema. Hospitalized for emphysema, collapsed lung and blood clots.
96012549	9/96	Took 9-12 pieces/d for 4 days. C/o constipation and burning sensation with urination. Admitted and treated for a kidney infection. Takes Ibuprofen, Zantac, Excedrin PM as needed.
96013739	10/96 11/96	50 pack year smoking history. Used gum 5 years ago for about a month. Diagnosed with lung cancer and metastatic breast cancer.
96013012	10/96 1/97 2/97	Developed stomach cramps and constipation on Nicorette. R/o Irritable Bowel Syndrome. Spouse reported in 1/97 that further workup revealed abdominal pain was due to a gallstone.
96016041	11/96	Chewed 36 pieces/d for 16 days; developed nausea, diarrhea, headache, sweats, impotence. Outcome attributed to nicotine overdose.
96016339	11/96 1/97	Admitted to ICU for shortness of breath and blackout. EKG changes noted with Nicorette use. History of angina and previous use of Nicorette without problems. No recurrence of symptoms after Nicorette d/c'd.
96016390	11/96	Used about 15 pieces of Nicorette instead of her usual 9-12 pieces/d. Experienced dizziness, nausea & vomiting. Presumed nicotine toxicity. H/o past MI, asthma, peptic ulcer; on several meds.
97009383	7/97	Used 2-3 pieces daily for about 3 weeks. Tachycardia on Nicorette and epinephrine for dental procedure. Treated in ER for continued tachycardia. Previously treated for panic attacks. Nicorette d/c'd. Improvement of symptoms but continued treatment for rapid heart rate.
97017322	8/97	Took Nicorette for 1-2 days, 5 pieces on the first day. Felt funny, woozy after dinner, felt he was going to fall and lost consciousness. Experienced pain in ribs and arm. Doctor noted BP 142/115. Admitted for observation; discharged on Lanoxin. H/o asthma. Smoked 2 packs/d for 47 years.
97029633	12/97 2/98 3/98	Patient alleged allergic reaction to yellow dye in Nicorette with confirmation via allergy testing. Medical records revealed allergic dermatitis, question of contact while cleaning out an old shed or a spider bite. Allergist did not confirm allegation.
98000719	1/98	Admitted for difficulty breathing; diagnosed with pulmonary edema. H/o quadruple bypass surgery, diabetes. Used Nicorette for 2 days.

Medical Officer's Comments:

A total of 15 15-Day Reports were submitted for the 2 mg gum, and 24 for the 4 mg gum. After exclusion of the fatal cases and duplicates, Table 4 lists 9 cases for the 2 mg gum and Table 5 lists 12 cases for the 4 mg gum. Most of the reports of adverse events described events known to be associated with Nicorette, such as, allergic reactions, cardiac reactions (increased heart rate, palpitations, extra beats), gastrointestinal symptoms (nausea, vomiting, gastritis, epigastric pain), and peripheral nervous system reactions (numbness, paresthesia).

There were 2 cases of nicotine toxicity in persons who were taking the 4 mg gum; 15 pieces in one individual (more than the usual amount taken) and 36 pieces in the other individual. Long-term use was reported for 3 people; 2 who took it for 4 years and the 69 y.o. female who used it for 15 years in Table 3.

Except for the 2 cases that experienced symptoms consistent with nicotine toxicity, it is difficult to attribute drug causality in most of these cases. There may have been other contributing factors in the individuals who developed cancer. In the 2 cases with cancer of the tongue, it is difficult to conclude that these persons developed the tumor because of Nicorette use, but it is noteworthy that both of them did use Nicorette far beyond the labeled duration; 4 years and 7 years. For several other cases, it is also probable that the underlying medical conditions, such as asthma, cardiac or gastrointestinal conditions, or headaches, and not Nicorette precipitated the reported events.

C. Other Adverse Events

(i) All Body Systems

Tables 6 and 7 provide a summary by body systems of the adverse events received for Nicorette gum 2 mg and 4 mg, from health professionals and consumers. The numbers reflect counts of events and not of individuals, from April 1, 1996 to August 31, 1998.

Table 6: ADEs by Body Systems reported by Health Care Professionals

Health Care Professional: 2 mg		Health Care Professional: 4 mg	
BODY SYSTEM	**COUNT**	**BODY SYSTEM**	**COUNT**
Application Site	2		
Autonomic Nervous System	3	Autonomic Nervous System	1
Body as a Whole General	16	Body as a Whole General	13
Cardiovascular General	1	Cardiovascular General	7
Central & Peripheral Nervous System	19	Central & Peripheral Nervous System	9
Collagen	2		
Endocrine	1		
Gastrointestinal System	24	Gastrointestinal System	31
Hearing and Vestibular System	2		
Heart Rate & Rhythm	4	Heart Rate & Rhythm	10
		Liver & Biliary	1
Metabolism & Nutrition	1	Metabolism & Nutrition	2
Musculoskeletal	3	Musculoskeletal	2
		Myocardium Endocardium Pericardium Valvular	3
Neoplasm	1	Neoplasm	4
Psychiatric	8	Psychiatric	9
		Resistance Mechanism	1
Reproductive Female	2		
Reproductive Male	1		
Respiratory System	13	Respiratory System	11
Skin And Appendages	13	Skin And Appendages	7
Special Senses Other	2		
Vision	1		
		WBC And Reticuloendothelial System	2
Unmapped Terms	5	Unmapped Terms	1
Total	124	**Total**	114

Medical Officer's Comments:

Nonserious ADEs were provided for the 2 mg and 4 mg original flavor Nicorette gum. Reports were tabulated by the source from which the information was received; the health care professional and the consumer. Only 1-2% of these ADE reports came from health care professionals; consumers reported the rest. Of the ADEs for both dosages reported by the health care professionals, the ones reported more often involved the GI system (such as nausea, stomatitis, mouth ulceration, mouth irritation, gingival bleeding, stomach ache, gagging, diverticulitis), Body as a Whole (such as pain, lack of efficacy, face edema, chest tightness), Central and Peripheral Nervous System (such as paresthesia circumoral, paresthesia, headache, burning skin, dizziness), Respiratory system (such as pharyngitis, throat sore, breathing difficulty, breath shortness, asthma), and Skin and Appendages (blisters, hives, rash).

Table 7: ADEs by Body Systems reported by Consumers

Consumer: 2 mg		Consumer: 4 mg	
BODY SYSTEM	**COUNT**	**BODY SYSTEM**	**COUNT**
		Application Site	2
Autonomic Nervous System	59	Autonomic Nervous System	80
Body as a Whole General	398	Body as a Whole General	461
Cardiovascular General	33	Cardiovascular General	32
Central & Peripheral Nervous System	681	Central & Peripheral Nervous System	749
Endocrine	2		
Gastrointestinal System	2332	Gastrointestinal System	2684
Hearing And Vestibular	8	Hearing And Vestibular	12
Heart Rate Rhythm	130	Heart Rate Rhythm	98
		Liver & Biliary	2
Metabolism & Nutrition	32	Metabolism & Nutrition	27
Musculoskeletal	35	Musculoskeletal	28
Myocardium Endocardium Pericardium Valvular	1		
Neoplasm	6	Neoplasm	1
		Platelet Bleeding Clotting	1
Psychiatric	917	Psychiatric	470
Reproductive Female	3		
Reproductive Male	9	Reproductive Male	4
Resistance Mechanism	12	Resistance Mechanism	9
Respiratory System	443	Respiratory System	455
Skin And Appendages	239	Skin And Appendages	234
Special Senses Other	28	Special Senses Other	32
Urinary System	12	Urinary System	22
Vascular Extracardial	5	Vascular Extracardial	5
Vision	25	Vision	16
WBC And Reticuloendothelial System	6	WBC And Reticuloendothelial System	3
Unmapped Terms	64	Unmapped Terms	58
Total	5480	**Total**	5485

Medical Officer's Comments:

Table 8 is a compilation of the ADEs most frequently reported by consumers, by dosage strength.

Table 8: ADEs more frequently reported by consumers, 2 mg and 4 mg

Body System	Included Term (events >50)
GI System **2 mg: 2332** **4 mg: 2684**	Nausea, Vomiting, Mouth Ulceration, Stomatitis, Heartburn, Stomach Upset, Gingivitis, Diarrhea, Stomach Ache, Hiccup, Tongue Pain, Mouth Ulceration, Mouth Irritation, Tongue Pain
	Included Term (events >30)
C NS & PNS **2 mg: 681** **4 mg: 749**	Dizziness, Headache, Burning Skin, Spasm Oropharyngeal, Paresthesia Circumoral, Light-headed Feeling, Numbness Localized
	Included Term (events >9)
Psychiatric **2 mg: 917** **4 mg: 470**	Drug Dependence (2 mg:712, 4 mg:307), Nervousness, Addiction Any Drug, Anxiety, Irritability, Insomnia
	Included Term (events>19)
Respiratory **2 mg: 443** **4 mg: 455**	Throat Sore, Pharyngitis, Coughing, Breathing Difficulty, Breath Shortness
	Included Term (events>20)
Skin & Appendages **2mg: 239** **4 mg: 234**	Rash, Blisters, Itching, Hives

Most of the adverse events mentioned were included in the sponsor's adverse event profile of Nicorette gum. Due to the nature of addiction to smoking cigarettes, some of the adverse experiences may be attributable to nicotine withdrawal effects or to nicotine toxicity. The majority of events reported by the health care professionals and consumers were GI events, with nausea, vomiting, stomach complaints, and mouth complaints as the most frequent ADE terms.

(ii) Body System: Psychiatric

There were 1019 consumer reports of drug dependence (2 mg: 712, 4 mg: 307). Thirty-nine counts of drug addiction/addiction any drug (2 mg: 25, 4 mg: 14) were also reported by consumers. In all, there were 9 health care professional reports of drug dependence (2 mg: 6, 4 mg: 3). There were no reports coded as drug addiction/addiction any drug from health care professionals.

The sponsor's definitions of the coded terms are as follows:
Drug dependence: product has been used for longer than the recommended duration.
Drug addiction/Addiction any drug: report of addiction or a suggestion of compulsive, uncontrollable dependence on the product to such a degree that cessation result in severe emotional, mental or psychological reactions

The sponsor also made the following points about the information received from consumers:

(1) The number reported is a number of events and not the number of individuals, since the same consumer can make several calls into the company for various reasons, and can also volunteer information about the duration of product use.
(2) The number of drug dependence reports is extremely low in comparison to the number of units sold:

[redacted]

With regard to events coded as dependence, the sponsor emphasized that any report of duration of use beyond the recommended duration is coded as dependence. However, dependence does not always imply continuous long-term use, as use may be broken up by periods of abstinence. The sponsor also stated that some consumers might have been advised by their physicians to continue to use of Nicorette beyond the labeled time frame. However, they were not able to provide a breakdown of the number of events by those where physician sanction was provided.

D. Worldwide Adverse Events

The sponsor stated that the flavor of the gum is normally not collected in the worldwide ADE reports. A summation of the reported number of ADEs by country is provided in Table 9. Data were provided only for the countries listed in the table; there was no information on additional foreign data. The information provided was also not listed by dosage strength of the gum.

Table 9: Reported Number of ADEs for OTC Nicorette in select countries

	Reported Number of ADEs	Calculated Number of Treated Patients
Canada	5	909,200
Switzerland	4	773,600
New Zealand	4	178,400
Australia	36	2,068,000
Germany	0	531,600
Norway	1	442,800
Sweden	13	3,224,000
Denmark	1	808,800
Great Britain	34	3,192,800
France	8	275,600
Belgium	1	259,600
Japan	0	-

The majority of terms listed for the ADEs for almost all of these countries were contained in the following body systems: GI, Body as a Whole, Central and Peripheral Nervous System, and Skin and Appendages,. The terms listed with greater frequency included: pruritus, rash, nausea, throat irritation, vomiting, mouth ulceration, stomatitis, abdominal pain, and headache. In France and Great Britain, there were 12 and 4 reports respectively, of drug dependence.

Medical Officer's Comments:

Limited conclusions can be drawn from the worldwide data on OTC Nicorette, except for the marked rarity of the number of events. The number of reports was received for varying time periods in each country, ranging from 1 to 9 years. It is unclear how the numbers of

treated patients were derived. Overall, however, the terms described for the AE were known and expected for Nicorette, and the pattern of distribution for the ADEs by body system, is expected as well.

Postmarketing Surveillance

In compliance with Phase IV Commitment, the sponsor has had a surveillance program in place to monitor, identify, and report the sale to and/or misuse of OTC Nicorette gum to persons less than 18 years of age. As of May 1998, 7 quarterly surveillance reports were submitted to FDA. The sponsor stated that the surveillance program has not detected any perceivable trends in product misuse. Information from the various components of the surveillance program is provided below.

A. Media Tracking

The sponsor monitored major wire services and 60 local and national newspapers throughout the country. A total of 816 individual media items were reported in the quarterly surveillance reports. The majority of reports were about promotional efforts for approved smoking cessation products, new treatments for smoking cessation (such as the approval of Zyban), alternate methods for smoking cessation (such as acupuncture, hypnosis, dietary supplements), increased awareness on the hazards of smoking, and increased pressures on the tobacco industry. Reports on underage usage were rare; if reported, they were on the use of NRTs to help adolescents quit smoking.

B. Consumer Tracking

The sponsor has been tracking consumers via the toll-free telephone number listed on product packaging. There has been an average of 4500 calls per quarter and a total of over 35,000 calls since OTC approval. The primary purpose is to provide guidance, answer consumer questions, and collect consumer complaints and adverse experiences. Information on use/misuse of the product by those less than 18 years were also documented. The sponsor reported that there has been no indication of inappropriate underage usage through this monitoring system. (As reported in the quarterly summaries, there were <10 inquiries per quarter from 3/97 to 6/98 on the appropriateness of use of Nicorette in those <18 years old.)

There was an average of 100 to 150 inquiries per quarter about the consequences of long-term use, or consumer expressions of personal concerns about dependence. The numbers of calls about long-term use and dependence have remained stable over the period of OTC availability.

The sponsor has also undertaken an on-going telephone survey via [redacted] of current and former smokers. A total of 8,530 interviews have been completed since the survey's inception. Since OTC availability, only 3 reports of usage in underage children were collected.

C. Theft Surveillance

Salesforce contact with retail trade has not identified any significant reports about the theft of Nicorette products by any age groups. The sponsor has provided a total of 44,150 merchandising racks to retailers as of February 1998. Most of these racks (82%) were equipped with locks. In this NDA submission, the sponsor stated that they have

discontinued shipment of the non-lockable racks and only ship out racks with locks to retailers.

D. Committed Quitters Program (CQP)
Consumers can enroll in the CQP by telephone. There are currently over 118,000 individuals enrolled. Approximately 0.4% of potential enrollees were under 18 years of age. Callers under 18 years old were informed that the product is not intended for their use and encouraged to discuss product use with their physicians.

E. Syndicated Surveys
The sponsor continues to engage in discussions to include specific questions on NRTs for smoking cessation on several national surveys. To date, questions have not been added to the National Survey of High School Students, the National Health Interview Survey, the Tobacco Use Supplement to the Current Population Survey, or the National Household Survey on Drug Abuse.

F. Safe and Drug Free Schools Coordinators Survey (SDFSC Survey)
A SDFSC Survey was conducted between October 1996 and February 1997. Interviews were completed with 562 SDFSC and 529 community members referred by the SDFSCs. Approximately 2.0% of interviewees volunteered any awareness of use of NRTs in adolescents. With prompting, a total of 46 anecdotal reports of adolescent use of NRTs were obtained from the 1,091 interviews completed. In-depth investigation of these reports showed no indication of abuse; most of the use was for quit smoking attempts.

G. Evaluation of Specific Reports of Potential NRT Abuse
The sponsor retained [redacted] to investigate any specific reports of abuse and/or misuse of NRT products. Thus, follow-up interviews were initiated with the 46 respondents who reported on the adolescent use of NRT products. Much of the information provided was secondhand from children and it was unclear if the children were actually using the products or were hearing about its use. The conclusions reached by [redacted] were that localized incidents of abuse may exist, but it was not a widespread problem. Overall, [redacted] did not obtain any direct evidence of a significant abuse problem with any of the NRTs.

Medical Officer's Comments:

The sponsor has initiated and continues to monitor for abuse/misuse of NRT products by under age adolescents. None of the information submitted from these postmarketing surveillance efforts are indicative of any widespread or even limited incidence of abuse/misuse of NRT products, and Nicorette specifically, by those less than 18 years of age. It may be difficult for these surveillance efforts to pick up small localized outbreaks, but significant events should be uncovered by the extensive tracking of the major wire and print services. It is unclear how representative the sample of 562 Safe and Drug Free Schools Coordinators are of the nation's school districts. SDFSC are people employed at the school district level and have the responsibility of coordinating district activities aimed at discouraging student drug use. It is not clear if these coordinators are the best source of information about the students' use/misuse/abuse of drug products since they may not have the one-on-one interaction that would be key to finding out about such activities. Overall, however, the concern about the

existence of widespread abuse of NRT products by underage adolescents, is not borne out by the information collected via postmarketing surveillance by the sponsor.

Conclusions

Nicorette Gum has had extensive worldwide marketing since initial approval as an Rx product. Since OTC approval, in the U.S. alone, over [redacted] boxes of the 2 mg and 4 mg gum (starter and refill sizes) have been sold. Nicorette Mint has been marketed in countries outside of the U.S. since 1991. Approximately [redacted] boxes of the 2 mg and 4 mg Mint Nicorette gum has been sold over the last 1-6 years in the 6 countries listed in Table 2 above.

The safety profile from postmarketing experience reveals a low rate of the number of adverse events when compared to the number of boxes of Nicorette sold. However that figure is not helpful with providing an estimate of adverse events to be expected per person, by the amount of Nicorette consumed. It is comforting to see that the majority of adverse events received reflect known expectations. In all, only 5 deaths were reported worldwide since Rx marketing. It is reasonable to conclude that in at least 4 of these reports, there were underlying medical conditions that could have contributed to the deaths. At the very most, the concern would be that the use of Nicorette in individuals with high cardiac risks should be monitored closely and the user should stop smoking entirely. As noted above, current labeling does refer individuals with medical risks to the physician before Nicorette use.

Information from worldwide postmarketing experience does not demonstrate any undue risk to the public from the use of OTC Nicorette gum. The concern raised for Nicorette Mint was the potential for the increased use of a nicotine containing product by naïve, underage adolescents, by the addition of mint flavoring which may make the gum more palatable. The results from sponsor's placebo-controlled abuse liability trial indicate no marked abuse liability of Mint Nicorette in adults and young adults compared to a prototypical drug of abuse, d-amphetamine, and no increase in abuse potential when compared to original flavor Nicorette gum. In addition, postmarketing surveillance efforts by the sponsor has not revealed much use/misuse/abuse by underage adolescents. However, these efforts should be continued for Nicorette Mint as well.

It is noted that there were over 1000 reports from health care professionals and consumers of long-term use of Nicorette (both dosage strengths) beyond the labeled duration of 12 weeks. These reports were called in through sponsor's toll free telephone number, and consumers were noted to state that they were "addicted" to the product. Consumers reported use of Nicorette from several months, to several years (as much as 10-12 years). Consumers also reported that they have used Nicorette while continuing to smoke. While long term use may include intermittent use over the long term because of repeated smoking cessation attempts, the concern is that consumers are switching addictions from cigarettes to Nicorette gum, or even using both at the same time. While it is difficult to assess the full extent of such inappropriate use of Nicorette from reports received via a consumer toll-free telephone system, and its significance, it may be prudent to consider reinforcing the existing statement by making it more prominent with bolding: **"Stop using Nicorette at the end of week 12. If you still feel the need for Nicorette, talk with your doctor."** If a stronger emphasis should be made, an additional statement could be added to the Warnings sub-section: **Stop use and see your doctor if you have** the need to use Nicorette at the end of week 12. However, this

issue of continued use beyond the labeled program duration may be pertinent to all OTC nicotine replacement products and can be discussed as a Class Labeling issue at a later time.

/S/

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

/S/

Linda M. Katz, M.D., M.P.H. 12/11/98
Deputy Director
DOTCDP

MEMORANDUM

TEAM LEADER(CSET/HFD-170) ADDENDUM TO MEDICAL REVIEW

DATE: November 13, 1998

APPLICATIONS: Supplemental NDA 18-612 Nicorette (nicotine polacrilex) 2 mg Gum
Supplemental NDA 20-066 Nicorette (nicotine polacrilex) 4 mg Gum

Deficiencies cited in the non-approval letter (October 6, 1996) for the original supplement included the need for evidence that a product which contains a dependence-producing active ingredient (nicotine) that is marketed in a more appealing manner (different sweetness or flavoring) than the original form does not present a risk as a gateway product into nicotine addiction for the non-smoking adolescent. Therefore, studies were needed to assess the differences in abuse liability that may arise from differences in product formulation. The data needed were to include the following:

A. Formal placebo-controlled abuse liability testing of the original and proposed flavors of Nicorette in populations of heavy smokers, light smokers, nonsmokers, adolescent smokers and flavored tobacco users.

A final study report for a formal placebo controlled abuse liability trial comparing the original flavor and mint flavor Nicorette 2 mg and 4 mg gum has been provided.

Sponsor maintains that study results indicate no marked abuse liability of mint flavor Nicorette in adults and young adults compared to the prototypical drug of abuse (d-amphetamine) and no increase in abuse potential compared to the original flavor Nicorette gum.

B. Palatability of the different formulations in these same populations:

A two-way crossover study designed to measure expectations and preferences of mint Nicorette compared to original flavor.

Sponsor maintains that results demonstrate a preference for mint flavor Nicorette compared to original, but with an overall palatability of both mint and original that is rated unfavorably. This would offer consumers a product with improved taste while still maintaining a strong pharmaceutical image that discourages casual use.

C. Assessment of extent of long-term use of different flavors of Nicorette when used for smoking cessation. SKB's ongoing surveillance programs for OTC sale of original flavor Nicorette 2 mg and 4 mg gum monitor for reports of product misuse. The program has not detected any trends in product misuse, including long term use of Nicorette. There has been no indication of misuse of the product.

The clinical study (No. MD-01011; Stitzer & Henningfield, Johns Hopkins University) was initiated to compare abuse liability of the mint gum to the original flavor of the gum. The study also compared abuse liability of the mint gum to smoking and d-amphetamine administration which have been shown to have positive abuse potentials in such assessments.

The Sponsor asserted that the study demonstrated that there was significantly less abuse liability for mint flavor Nicorette compared to the positive control (d-amphetamine), that there was no greater abuse liability for mint flavor Nicorette than original flavor and that there was no significant interaction between age and dose on abuse liability measures for mint flavor Nicorette.

The study sought to determine the abuse potential of the mint flavor Nicorette by comparing response on measures of abuse liability to those reported after ingesting a drug with known abuse liability (d-amphetamine). Also, the abuse liability of mint flavor Nicorette was further assessed by comparing the dose-response curves of mint flavor Nicorette to those of original flavor Nicorette, which has been demonstrated to have little abuse potential. Finally, abuse liability rating of mint flavor Nicorette by older and younger adults were compared to determine if the mint flavor gum is particularly appealing to younger adults.

Study No. MD-01011 was a randomized, double blind, placebo controlled study using a crossover design. Subjects were recruited to participate in this 13 session outpatient study. The 13 session days (separated by at least 24 hours) consisted of 3.5 hour sessions in which subjects swallowed 2 capsules and 1.5 hours later, chewed 2 pieces of gum or smoked a cigarette. The first session was a practice session. During each session, subject-rated questionnaires were presented before and after drug adminsitration which assessed abuse liability, gum palatability and tobacco withdrawal and craving. Abuse liability was evaluated by scores on 3 primary measures of abuse liability for gum that approximate those observed for d-amphetamine, and was also evaluated by assessing dose-related increases in scores on these measures for mint flavor Nicorette compared to the original flavor. Comparative abuse liabilities were indicated by 3 key variables:

1. Drug liking: response to the question "Do you like the drug effect?" (100 mm VAS).
2. Positive Drug Effect: Response to the question "Does the drug have any good effects?" (100 mgVAS).
3. MBG: The Morphine-Benzedrine Group (MBG) subscale score of the Addiction Research Center Inventory (ARCI) which is a measure of "euphoria". Scores on this measure have been shown in other studies to increase after ingestion of abused drugs including morphine, amphetamines and intravenous nicotine.

RESULTS

1. From Table 1 (in answer to the question: "Would you chew this gum just to get the drug effect?") the following relative order of preference was obtained: Amphetamine-Orig = Amphetamine-Mint > Placebo-Mint > Nicotine-Mint = Nicotine-Orig > = Placebo-Orig.

2. From Table 2 (in answer to the question: "How sweet is the gum?") the following order of preference (that is more sweet ranked higher) were obtained: Amphetamine-Mint > Placebo-Mint>Placebo-Orig>Nicotine-Mint=Amphetamine-Orig>Nicotine-Orig.

3. From Table 3 (in answer to the question: "How much do you like the gum overall?") the following order of preference was obtained: Amphetamine-Mint > Placebo-Mint>Placebo-Orig>Nicotine-Mint=Amphetamine-Orig>Nicotine-Orig. Amphetamine-Orig=Amphetamine-Mint>Placebo-Mint>Placebo-Orig>Nicotine-Mint>Nicotine-Orig

4. The following order of preference was obtained for drug liking (Table 4), in answer to the question: "Do you like the Drug Effect?".

Amphetamine-Mint >> Amphetamine-Original >> Nicotine-Mint = Nicotine-Original >> Placebo-Mint = Placebo-Original >> Cigarette.

5. From Table 5, which demonstrates the euphoria responses on the MBG subscale of the ARCI scale, the following responses were obtained:

A. Of 24 subjects, mint-nicotine rated higher than mint-placebo in 16 subjects, rated lower in 2 subjects, and rated no difference in 6 subjects. Similar responses were obtained for original-placebo and original-nicotine products. Of 24 subjects, original-nicotine rated higher than original-placebo in 15 subjects, rated lower in 2 subjects, and rated no difference in 7 subjects.

The breakdown of responses for older and younger adult categories did not show a significant difference as well. More younger adults than older adults did not record differences between placebo and active drug for the mint and original formulations (mint: 4 vs 2; original: 5 vs. 2). There was a likely dose response to the different Nicorette dosages ingested which was responsible for the variable responses among subjects.

CONCLUSION:

In past reviews of similar studies, we had determined that the most reasonable way to interpret this sort of data (because of subject to subject variability in responses) was to analyze individual responses. For drug liking and taste responses, we have focused on individual preferences in rank order of how each individual subject responded by formulation type, i.e., the mint flavored vs the orginal flavored, and by substance type, i.e., placebo, vs nicotine vs. amphetamine.

For the responses of the MBG subscale of the ARCI, we simply observed the number of subjects who responded positively, negatively or without change from placebo. Very similar patterns were obtained with mint nicotine and original nicotine products relative to their respective placebos. The major difference between older and younger adult populations was that fewer young adults recorded differences from placebo.

There is some indication of preference for mint formulations as demonstrated by the two amphetamine controls. Amphetamine products received greater liking scores (that is, they were preferred) than nicotine. However, virtually no differences in preference were apparent between mint-nicotine and original nicotine formulations. There was a clear separation of the placebo formulations from the nicotine-containing formulations. This indicates a likely abuse potential (as indicated by drug liking scores) for the nicotine products which lie between those of placebo and amphetamine. Differences due to taste were evident in some responses in which the mint formulation was favored.

As this study further supports the view that Nicorette has an abuse liability, the Sponsor should be asked to assess the success of the restricted sales of Nicorette products to minors and determine extent of compliance by pharmacies regarding this part of the label.

/S/ 11-13-98

Michael Klein, Ph.D., Team Leader (CSET, HFD-170) (Date)

TABLE 1. QUESTION: "Would you chew this gum just to get the drug effect?"

Subj #	mint-active	mint-placbo	orig.-active	orig-placebo	amphet-mint	amphet-orig
1	0 (4)	3 (1)	0 (4)	0 (4)	0 (4)	0 (4)
2	8 (5)	55 (2)	6.3 (6)	15 (4)	51 (3)	82 (1)
3	20.3 (3)	1 (5)	11.7 (4)	52 (1)	0 (6)	36 (2)
4	18.3 (3)	0 (5.5)	1.3 (4)	0 (5.5)	32 (2)	64 (1)
7	23 (6)	47 (2)	33 (5)	46 (3)	41 (4)	73 (1)
8	54.7 (3)	89 (1)	83.7 (2)	0 (5.5)	0 (5.5)	1 (4)
9	81 (2)	1 (5)	84 (1)	1 (5)	1 (5)	4 (3)
11	28.3 (3)	40 (2)	14.3 (5)	1 (6)	26 (4)	65 (1)
12	45.7 (5)	75 (2)	27.7 (6)	46 (4)	76 (1)	60 (3)
14	30.7 (4)	6 (6)	59.3 (2)	27 (5)	61 (1)	31 (3)
15	2 (3.5)	2 (3.5)	3.3 (2)	0 (5.5)	0 (5.5)	45 (1)
16	0 (3.5)	0 (3.5)	0 (3.5)	0 (3.5)	0 (3.5)	0 (3.5)
18	3.3 (4)	13 (3)	26.3 (2)	0 (5.5)	73 (1)	0 (5.5)
20	49.3 (2)	21 (5)	39.3 (3)	8 (6)	56 (1)	25 (4)
22	13.7 (1)	0 (4.5)	0 (4.5)	0 (4.5)	0 (4.5)	4 (2)
24	0 (4)	0 (4)	0 (4)	0 (4)	12 (1)	0 (4)
106	27.7 (3)	100 (1)	0 (5)	0 (5)	86 (2)	0 (5)
117	0 (4.5)	2 (1)	0 (4.5)	0 (4.5)	1 (2)	0 (4.5)
119	0 (4)	1 (1)	0 (4)	0 (4)	0 (4)	0 (4)
121	3.7 (1)	0 (4)	0 (4)	0 (4)	0 (4)	0 (4)
123	.3 (3)	0 (5)	2.3 (1)	1 (2)	0 (5)	0 (5)
205	0 (3.5)	0 (3.5)	0 (3.5)	0 (3.5)	0 (3.5)	0 (3.5)
210	2 (5)	0 (6)	19.3 (3)	18 (4)	42 (1)	41 (2)
313	0 (3.5)	0 (3.5)	0 (3.5)	0 (3.5)	0 (3.5)	0 (3.5)
Rank tot	83.5	80.0	86.5	102.5	77.0	74.5
Rank avg.	3.5	3.3	3.6	4.3	3.2	3.1

Maximum individual responses & rank order preference. Rankings (average) are in parenthesis ().

TABLE 2. QUESTION: "How sweet is the gum?"

Subj #	mint-active	mint-placbo	orig.-active	orig-placebo	amphet-mint	amphet-orig
1	10.3 (5)	48 (1)	3 (6)	11 (4)	27 (2)	26 (3)
2	4.3 (5)	81 (1)	6 (4)	4 (6)	14 (3)	73 (2)
3	1.7 (6)	26 (2)	8 (3)	2 (5)	32 (1)	5 (4)
4	38.3 (4)	78 (1)	6.3 (6)	54 (3)	66 (2)	25 (5)
7	31.3 (3)	60 (2)	20.7 (4)	17 (5)	74 (1)	14 (6)
8	75.7 (2)	21 (3)	6 (4)	4 (6)	94 (1)	5 (5)
9	6 (1)	1 (5)	1 (5)	1 (5)	2 (3)	3 (2)
11	24.7 (5)	42 (3)	16.3 (6)	44 (2)	58 (1)	30 (4)
12	36 (4)	61 (2)	9 (6)	53 (3)	79 (1)	21 (5)
14	32.3 (5)	72 (2)	16 (6)	41 (4)	79 (1)	61 (3)
15	40.7 (4)	61 (3)	0 (6)	82 (1)	78 (2)	12 (5)
16	0 (4.5)	0 (4.5)	12.7 (1)	3 (2)	0 (4.5)	0 (4.5)
18	4.3 (5)	30 (4)	2.3 (6)	60 (2)	72 (1)	45 (3)
20	23.7 (6)	37 (3)	25 (5)	40 (2)	46 (1)	32 (4)
22	0 (4)	14 (1)	0 (4)	0 (4)	0 (4)	0 (4)
24	0 (4)	0 (4)	0 (4)	0 (4)	12 (1)	0 (4)
106	8.3 (3)	48 (1)	4.3 (4)	0 (6)	47 (2)	1 (5)
117	3.3 (5)	76 (1)	14.7 (3)	3 (6)	34 (2)	6 (4)
119	23.7 (5)	43 (3)	17.7 (6)	80 (2)	27 (4)	83 (1)
121	2.3 (5)	7 (2)	1.3 (6)	5 (3)	9 (1)	3 (4)
123	16 (3.5)	16 (3.5)	0.3 (6)	24 (2)	46 (1)	10 (5)
205	16.3 (1)	8 (2)	0 (4.5)	0 (4.5)	0 (4.5)	0 (4.5)
210	27.7 (3)	77 (1)	3.3 (5)	0 (6)	76 (2)	12 (4)
313	5.7 (4)	0 (6)	11.7 (2)	4 (5)	6 (3)	31 (1)
Rank tot	97	61	112.5	92.5	49	96.5
Rank avg.	4.0	2.5	4.7	3.8	2	4

Maximum individual responses & rank order preference. Rankings (average) are in parenthesis ().

TABLE 3. QUESTION: "How much do you like the gum overall?"

Subj #	mint-active	mint-placbo	orig.-active	orig-placebo	amphet-mint	amphet-orig
1	4.7 (3)	0 (5)	0 (5)	0 (5)	13 (1)	9 (2)
2	5.3 (5.5)	47 (3)	5.3 (5.5)	7 (4)	56 (2)	88 (1)
3	28 (3)	9 (6)	16.7 (5)	43 (1)	20 (4)	37 (2)
4	27.7 (5)	70 (2.5)	3.7 (6)	54 (4)	81 (1)	70 (2.5)
7	27 (6)	50 (2)	41 (4)	28 (5)	49 (3)	68 (1)
8	50 (2)	75 (1)	13 (3)	3 (4.5)	1 (6)	3 (4.5)
9	57.3 (2)	1 (5.5)	84 (1)	1 (5.5)	2 (4)	3 (3)
11	36.3 (4)	27 (5)	20 (6)	40 (3)	51 (2)	61 (1)
12	46.3 (4)	66 (2)	23.7 (6)	32 (5)	79 (1)	56 (3)
14	37.3 (5)	71 (1.5)	61 (4)	32 (6)	71 (1.5)	66 (3)
15	28 (5)	80 (1)	1.3 (6)	61 (4)	78 (2)	62 (3)
16	0 (5.5)	4 (2)	0 (5.5)	3 (3.5)	3 (3.5)	26 (1)
18	2 (6)	79 (1)	3 (5)	69 (3)	7 (4)	71 (2)
20	37.7 (4)	34 (5)	28.3 (6)	58 (3)	77 (1)	66 (2)
22	0 (4.5)	4 (2)	0 (4.5)	0 (4.5)	33 (1)	0 (4.5)
24	0 (3.5)	0 (3.5)	0 (3.5)	0 (3.5)	0 (3.5)	0 3.5)
106	16.7 (5)	100 (1.5)	15.7 (6)	62 (3)	100 (1.5)	51 (4)
117	0 (5.5)	56 (2)	0.3 (4)	0 (5.5)	62 (1)	39 (3)
119	0 (5.5)	1 (3.5)	0 (5.5)	4.9 (1)	1 (3.5)	30 (2)
121	0 (3.5)	0 (3.5)	0 (3.5)	0 (3.5)	0 (3.5)	0 (3.5)
123	2 (4)	15 (2)	0 (6)	1 (5)	42 (1)	12 (3)
205	13.3 (1)	0 (4)	0 (4)	0 (4)	0 (4)	0 (4)
210	13.3 (5)	10 (6)	21.3 (3)	21 (4)	47 (2)	52 (1)
313	11.7 (2)	0 (5)	6.3 (3)	0 (5)	0 (5)	48 (1)
Rank tot	99.5	75.5	111.0	95.5	62.0	61.0
Rank avg.	4.2	3.2	4.6	4	2.6	2.5

Maximum individual responses & rank order preference. Rankings (average) are in parenthesis ().

TABLE 4. QUESTION: Do you like the Drug Effect?

Subject	mint-active	mint-placebo	cigarette	orig-active	orig-placebo	amphet-mint	amphet-orig
1	0 (6)	0 (6)	0 (6)	1 (4)	8 (3)	52 (1)	17 (2)
2	79 (3)	75 (4)	6 (5)	3 (6)	0 (7)	99 (1.5)	99 (1.5)
3	34 (4)	1 (6)	0 (7)	27 (5)	57 (2)	71 (1)	46 (3)
4	2 (3)	1 (5.5)	1 (5.5)	1 (5.5)	1 (5.5)	100 (1)	96 (2)
7	20 (7)	52 (3)	53 (2)	35 (6)	46 (5)	49 (4)	82 (1)
8	88 (2)	87 (3)	0 (6.5)	3 (4.5)	0 (6.5)	100 (1)	3 (4.5)
9	82 (2)	2 (4.5)	0 (7)	83 (1)	1 (6)	2 (4.5)	9 (3)
11	20 (4)	1 (6.5)	53 (2)	11 (5)	1 (6.5)	46 (3)	63 (1)
12	56 (5)	69 (3)	45 (7)	48 (6)	62 (4)	86 (1)	72 (2)
14	29 (3)	17 (5.5)	2 (7)	58 (2)	24 (4)	73 (1)	17 (5.5)
15	0.3 (6)	5 (5)	0 (7)	33 (3)	41 (2)	86 (1)	32 (4)
16	2 (4)	0 (6)	0 (6)	11 (3)	0 (6)	100 (1.5)	100 (1.5)
18	2 (6)	6 (5)	0 (7)	19 (4)	90 (1)	88 (2)	81 (3)
20	53 (2)	34 (5)	14 (7)	39 (3.5)	33 (6)	74 (1)	39 (3.5)
22	0 (4.5)	0 (4.5)	0 (4.5)	0 (4.5)	0 (4.5)	28 (1)	0 (4.5)
24	0 (5)	0 (5)	0 (5)	0 (5)	100 (1.5)	0 (5)	100 (1.5)
106	21 (3)	100 (1.5)	0 (6)	16 (4)	0 (6)	100 (1.5)	0 (6)
117	0 (6)	1 (2)	0 (6)	.3 (4)	1 (2)	1 (2)	0 (6)
119	5 (1)	1 (2)	0 (5.5)	.3 (3)	0 (5.5)	0 (5.5)	0 (5.5)
121	0 (6.5)	11 (1)	9 (2)	6 (3)	1 (5)	0 (6.5)	4 (4)
123	3 (1)	0 (5.5)	0 (5.5)	.3 (3)	1 (2)	0 (5.5)	0 (5.5)
205	0 (4)	0 (4)	0 (4)	0 (4)	0 (4)	0 (4)	0 (4)
210	.3 (5)	0 (6.5)	0 (6.5)	35 (3)	15 (4)	55 (2)	75 (1)
Rank Tot	93	100	127.5	92	99	57.5	75.5
Rank Av.	4.04	4.347	5.5	4.00	4.304	2.5	3.28

Maximum individual responses & rank order preference. Rankings (average) are in parenthesis ().

TABLE 5. ARCI MBG RESPONSES 90 MINUTES

Subject	mint-active	mint-placebo	cigarette	orig-active	orig-placebo	amphet-mint	amphet-orig
1 older	(2 mg) 2; (4mg) 2; (8mg) 1	2	2	(2mg) 2; (4mg) 0; (8mg 0	1	15	2
2 older	2; 1; 0	1	1	2; 2; 2	2	4.79	2
3 older	1; 3; 0	1	1	1; 4; 0	1	1	3
4 older	7; 10; 6	7	4	7; 5; 6	4	13	7
7 older	0; 7; 2	1	2	0; 0; 1	14	5	9
8 older	0; 3; 1	1	3	1; 0; 0	2	5	1
9 older	13;13;12	13	13	13;13;13	13	14	13
11 older	1;1;2	1	0	1;1;0	0	1	3
12 older	2;2;10	16	3	5;14;15	6	11	4
14 older	10;13;9	7	6	13;14;12	7	15	5
15younger	1;2;1	1	1	2;11;1	2	5	10
16younger	0;2;0	4	0	1;1;1	0	16	16
18 older	11;11;6	2	4	11;10;11	3	5	3
20younger	9; 14; 5	4	7	10;9;10	1	13	14
22younger	12;15;12	13	13	15;12;14	10	8	14
24younger	11;3;9	1	1	9;1;12	12	1	14
106younger	5;5;5	5	5	5;5;5	5	5	5
117 older	9;4; 9	7	9	3;9;9	0	4	5
119younger	2;1;3	3	1	1;3;2	2	4	1
121younger	1;1;1	0	1	1;1;1	0	1	1
123younger	0;0;0	0	0	0;0;0	0	5	0
205younger	0;0;0	0	0	0; 0; 0	0	0	8
210younger	14;15;11	14	15	15; 9; 15	13	16	15
313younger	0;2;0	0	0	0; 0; 0	0	0	4

Medical Officer Review

NDA #:	18612 (Supplement # SE4-025) 20066 (Supplement # SE4-007)
Drug:	Nicorette (Nicotine Polacrilex) 2mg and 4mg
Sponsor:	SmithKline Beecham Consumer Healthcare
Proposed Indication:	Addition of Mint Flavor Nicorette 2 and 4mg OTC
Submitted:	15 May 1998
Reviewer:	E Douglas Kramer
Peer Reviewer:	Michael Klein Celia Winchell
CSO:	Indira Kumar
Dates:	15 May 1998 Submitted 18 May 1998 Received CDER 13 Nov 1998 Review Completed
File Name:	

1. Background

Nicorette (nicotine polacrilex) is a nicotine-containing tobacco-flavored gum-like nicotine dosage form that provides smokers with buccally administered nicotine as an aid to smoking cessation. Nicorette 2mg was approved as a prescription smoking cessation aid in 1984. The 4mg strength was approved as a prescription product in 1992.

In February 1996 both 2 and 4 mg strengths were approved for OTC sale. The data on which this approval was based included data from 2 "OTC usage" trials in adult smokers. The approval included a prohibition on sales to minors, including sales from vending machines or by other means where the buyer's age could not be verified. There was also an extensive phase 4 surveillance/marketing program intended to allow the sponsor to market the product to "committed quitters" while allowing them to detect and intervene in instances of adolescent misuse or abuse of Nicorette. This program included a commitment to "conduct a surveillance study designed to identify and report on sale to or use by people less than 18 years of age." These steps were taken to try to address the risk that Nicorette might become a gateway product to nicotine addiction if the product were to become widely available to adolescents.

Later that year, the sponsor filed an NDA supplement requesting approval for Mint and Citrus flavored Nicorette. The goal of that supplement was to provide smokers with more acceptable flavors than the Original "tobacco" flavored product. That supplement included chemistry and manufacturing information and a pharmacokinetic study. That supplement was not approved. The efficacy of the product was not in question. However, the sponsor was asked to provide data to address concerns that an improvement in the palatability of the product might change the adolescent appeal/abuse liability of Nicorette.

This NDA supplement requests approval for the Mint flavor Nicorette. The supplement contains the chemistry and biopharmaceutics information that was present in the Original NDA supplement. An abuse liability study (MD01011) of the Mint and Original formulations is included as well as a marketing study (S1330011). A report from the Swedish Institute for Tobacco Studies on Adolescent Use of NRT Products (which includes data on both Mint and Original flavor Nicorette) and Qualitative Youth Appeal Assessments (based on focus groups of teenagers) are also included.

The sponsor intends to continue their current marketing program with the proposed Mint Nicorette. The program includes:

- restricting sales to individuals 18 years and over.
- Ensuring age verification programs are used where NRT is distributed.
- Restricting sale from vending machines or from any source where proof of age cannot be verified.

- Where violations of the conditions of sale are identified, the retailer will be retrained to bring the store into compliance, or, distribution t the outlet in question will cease.
- Targeting advertisements to adult smokers.
- Providing Spanish language labeling by request, as well as outreach efforts to other ethnic audiences.
- Trial size or sample packs will not be offered.
- Packaging of each gum piece in a child resistant blister.
- Restricting distribution to drugstores, mass merchandisers and supermarkets where other OTC drugs are sold. The products will not be distributed to other channels, including convenience stores unless it is demonstrated that these channels pose no greater risk than traditional outlets.
- availability of lockable storage cabinets for shelving of NRT at retail outlets.
- availability of a free smoking cessation program with a toll free phone number.

The sponsor is also proposing to continue their current program of post marketing surveillance for 3 years following approval. This program includes media surveillance, consumer tracking, retail theft surveillance, the sponsor's Committed Quitters Program, a survey of safe and drug free schools coordinators and continued efforts to include questions on Nicorette use by adolescents in national syndicated surveys of adolescent drug use. [It should be noted that while the agency had no objection to the sponsor's desire to try to meet their phase 4 commitment to identify and report on use of NRT by adolescents by collaborating with other institutions, this commitment was not contingent on the sponsor's ability to find a willing collaborator. If they were not successful in identifying a partner for a joint venture, the commitment still needed to be fulfilled.]

2. Material Reviewed

The following material is reviewed:

- The Abuse Liability Study, MD-01011, *"Nicotine Chewing Gum Comparison"* (volumes 4 to 11 of the NDA). A full report of this study is submitted. This study is reviewed in detail, including the sponsor's electronic data. Case Report Forms (CRFs) and Case Report Tabulations (CRTs) were not submitted for this study as data was captured directly by computer in the laboratory.
- The Marketing Study, S1330011, *"A Two Way Crossover Study To Measure Subject Expectations And Preference For Nicorette Nicotine Gum (Mint Flavor) Compared To*

Nicorette Nicotine Gum (Original Flavor) In Light And Heavy Smokers" (volumes 11 and 12 of the NDA). CRFs and CRT's are not included.

- The report *"Adolescent Use Of NRT-Products (Data From The 1997 Survey Of Drug Use Among 16 Year Old Boys And Girls In Sweden)."* Swedish Institute for Tobacco Studies report, (volume 25 of the NDA).

- Qualitative Youth Appeal Assessments (volumes 13 to 24 of the NDA). The submission includes videotapes and transcripts from 10 of 13 adolescent focus groups. (Videos/transcripts for groups in April 1995 were not available).

3. Foreign Marketing History

The 4mg strength of Mint Nicorette is marketed in 30 countries, Rx in 9 and "OTC" in 21. A significant difference exists, however, in the definition of "OTC" in other countries compared to the US. The definition of "OTC" in all countries where it is available "OTC" is pharmacy only dispensed under pharmacist's supervision.

General information on foreign sales of Nicorette is presented in volume 1 of the NDA and specific sales figures are presented for a number of countries in response to an information request from DODP. Mint Nicorette was introduced in the UK in 1993. Since that time, total sales (Measured by IMS sales from wholesaler to pharmacy) rose from approximately [redacted] The proportion of Mint sales rose from 9% in 1993 to 21% in 1996 and 25% in 1997. In Sweden in 1993 and 1994 sales of Mint Nicorette were 32 and 26% with Original Nicorette sales accounting for the difference. Following the introduction of Citrus Nicorette to the Swedish market in 1995, the proportion of Mint Nicorette sales remained stable at about 25% of the market and Original Nicorette accounted for 60 to 65%.

This data suggests that Original Nicorette has continued to be the predominant flavor even in markets where more than one alternative exists. While an increase in use of Nicorette appears to have coincided with the launch of Mint Nicorette in the UK, Original Nicorette is still the predominant marketed form in both the UK and Sweden.

4. Chemistry

The flavoring and sweetening agents found in Mint and Original Nicorette are listed in the following table:

Table 1 Flavoring and Sweetening Agents In Mint and Original Nicorette

	Original 2mg	Original 4mg	Mint 2mg	Mint 4mg
Nicotine resin 20%				
Sorbitol powder				
Sorbitol 70%				
Flavor for smoker				
Haverstroo				
Xylitol				
Peppermint oil				
Levomenthol				

There is some concern about the switch in sweeteners from sorbitol to xylitol. According to the MicroMedex (DrugDex) drug consult on artificial sweeteners (revised 6/94) artificial sweeteners are not all the same relative sweetness. Although the milligram amounts of sweetener are roughly comparable between the Original and Mint formulations, the products may differ appreciably in perceived sweetness. This potential difference is one of the concerns to be addressed in this supplement.

5. Animal Pharmacology

The NDA contains no new preclinical pharmacology.

6. Proposed Indication(s), Dosage Form, and Strength(s), Route of Administration, and Directions for Use

The indication and use of the Mint flavor will be the same as the approved indication and use of Original flavor Nicorette:

Action: Stop Smoking Aid
Use: To reduce withdrawal symptoms, including nicotine craving, associated with quitting smoking.

The 2 mg gum is recommended for persons smoking under 25 cigarettes per day
The 4mg gum is recommended for persons smoking 25 or more cigarettes per day.

The maximum duration of treatment is 12 weeks and the maximum number of doses per day is 24. Using 1 piece every 1 to 2 hours is recommended for the first 6 weeks; 1 piece every 2 to 4 hours is recommended for weeks 7 to 9; 1 piece every 4 to 8 hours is recommended during weeks 10 to 12.

The sponsor reports that the only changes in the labeling will be to list the different inactive ingredients in the new product and to identify the new product as Mint.

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7. Summary of Human Pharmacokinetics

The following table presents average nicotine pharmacokinetic parameters for 2 and 4 mg Nicorette and cigarettes.

Table 2 Average Pharmacokinetics of Nicotine Gum and Cigarettes.

Delivery System (sub. no.)	Strength Release Rate	AUC (0-inf) ng*hr/mL (%CV)	Cmax ng/mL (%CV)	Tmax Hrs (%CV)	Absolute Bioavail. % (%CV)
Gum Nicorette (n=24)	2 mg (30 minutes)	17.5 ± 5.9 (34%)	6.0 ± 2.4 (40%)	0.52 ± 0.13 (26%)	78 ± 49 (63%)
	4 mg (30 minutes)	27.2 ± 10 (39%)	9.9 ± 3.9 (39%)	0.42 ± 0.08 (20%)	55 ± 20 (36%)
Cigarette (n=10)	1 1/3 cig. (9 minutes)	34.4 ± 22.4 (65%)	15.8 ± 5.9 (37%)	0.17 ± 0.06 (35%)	

Note: Data is taken from "Joint Abuse Liability Review of Nicotine Nasal Spray" (NDA 20385) as prepared by Ruth Stevens, PhD. The table lists the comparative pharmacokinetics parameters (Mean ± SD) among nicotine gum and cigarettes after a single dose administration. The mean Cmax listed for NNS was taken from the first dose of the multiple dose study and is not corrected for baseline nicotine concentrations. The data are not corrected for baseline nicotine concentrations.

Bioequivalence Study (Mint and Citrus Nicorette): The pharmacokinetic study involved 20 healthy male and female smokers aged 19-46 who each received 1 strength of Mint, fruit, or regular flavor Nicorette hourly in each of 6 12-hour test sessions of an open crossover study. The sponsor reports demonstrating both bioequivalence and dose-proportionality. No serious or unexpected adverse events were reported for any of the formulations tested. Subjective ratings of gum acceptability are not reported.

The pharmacokinetics of Nicorette in smoking adults are significantly different from those of cigarettes

8. Efficacy Findings

This NDA contains no new information about the efficacy of Mint Nicorette in smoking cessation.

9. Safety Data

The studies and information in this NDA address the safety of the new formulation of Nicorette as regards the effect of improved palatability on the abuse liability and adolescent appeal of the Mint vs. the Original flavor.

9.1. Abuse Liability Study (MD 01011)

9.1.1. Investigator(s) /Location /Dates

Maxine Stitzer, PhD
Jack Henningfield, PhD
Johns Hopkins University School of Medicine
Behavioral Pharmacology Research Unit
5510 Nathan Shock Dr
Baltimore MD 21224

Study Start Date: 08 Aug 1997
Study Completion Date: 28 Feb 1998

9.1.2. Study Plan

This was a single-site Latin-square, 13-session placebo and active-controlled outpatient study comparing the abuse liability of 2, 4 and 8mg doses of Mint and Original Flavor Nicorette with d-amphetamine, and placebo Mint and Original Nicorette in adult smokers. Subjects received at most 1 active drug in each session. During each session subjects smoked a cigarette, swallowed an oral capsule (20mg amphetamine or placebo), and received 2 pieces of gum (placebo, 2, 4, or 8mg of nicotine, as mint or original flavor Nicorette) over 15 minutes in a timed chewing procedure. The capsule administration and gum chewing were timed such that the expected pharmacological peak of the drug effects from nicotine and amphetamine would coincide at about 2 hours after administration. Marketed confectionery gums were tested in a practice session and one experimental session to assess palatability. A second cigarette was smoked (in lieu of gum chewing) for a final experimental session. Outcome measures were based on traditional abuse liability assessment tools (e.g. drug liking, Addiction Research Center Inventory, [ARCI]). A behavioral economics interview was also included in the study.

9.1.3. Objective(s) Rationale

1) Evaluate the abuse liability of mint flavor Nicorette relative to d-amphetamine (20mg/70kg), a drug with known abuse liability.
2) Evaluate the abuse liability of mint flavor Nicorette relative to original flavor Nicorette.
3) Compare the abuse liability of mint flavor Nicorette between younger and older adults.

9.1.4. Population

Major inclusion criteria included:

1) Community volunteers, 50% aged 18-21, 50% aged 22-50.
2) Current cigarette smoking.
3) Baseline smoking rate of 15 or more cigarettes per day.

4) Baseline afternoon exhaled CO>15ppm.

Major exclusion criteria included:

1) Chronic health problems or psychiatric conditions.
2) History of or active cardiovascular disease, fainting spells, seizures or head trauma.
3) Regular use of prescription medication.
4) Self-reported use of illicit drugs within 30 days prior to screening or positive urine drug screen.

9.1.5. Design

The order of dosing was randomly assigned based on age using 2 12x12 Latin squares. The different treatment conditions are outlined in the table below.

Table 3 Treatment Conditions Studied

Session Number	Session Type	Total Capsule Dose	Nicorette Dose*	Nicorette Dose*	Gum Flavor	Regular Cigarette
1	Practice	Placebo	N/A	N/A	Confectionery fruit**	No
2	Experimental	Placebo	Placebo	Placebo	Original	No
3	Experimental	Placebo	2mg	Placebo	Original	No
4	Experimental	Placebo	4mg	Placebo	Original	No
5	Experimental	Placebo	4mg	4mg	Original	No
6	Experimental	Placebo	Placebo	Placebo	Mint	No
7	Experimental	Placebo	2mg	Placebo	Mint	No
8	Experimental	Placebo	4mg	Placebo	Mint	No
9	Experimental	Placebo	4mg	4mg	Mint	No
10	Experimental	20mg/70kg amphetamine	Placebo	Placebo	Original	No
11	Experimental	20mg/70kg amphetamine	Placebo	Placebo	Mint	No
12	Experimental	Placebo	N/A	N/A	Confectionery mint**	No
13	Experimental	Placebo	None	None	N/A	Yes

Based on table 9.1.1 of the sponsor's study report.
*In each session two pieces of gum are chewed; thus 8mg Nicorette conditions involved chewing two pieces of 4mg Nicorette.
**These are marketed gums included for practice with the chewing procedure (Session1) or palatability comparison (Session12).

The timing of study assessments is shown in the following table:

Table 4 Timing of Study Assessments (minutes)

Time (minutes)	-15	0	30	70	90	105	110	115	120***	150	180
Assessments											
ARCI	X				X				X		X
Agonist Analog	X				X				X	X	X
Behavioral Economics Interview					X				X**		
Digit Symbol Substitution	X				X				X		
Drug Effect Scale							X*	X*	X	X	X
Gum Scale							X*	X*	X		
Actions											
Capsule administration		X									
Smoke first cigarette			X								
Begin monitoring of vital signs				X							
CO level	X				X						
Begin gum administration						X					
End gum administration									X		
Smoke 2nd Cigarette (only Session 13)								X			

Based on table 9.5.1 of the sponsor's study report

*Assessments at 11 0 and 115 minutes were not administered during session 13.

**Last measure collected in the battery of assessments administered at 120 minutes.

*** Measures at 120 minutes or immediately after finishing second cigarette.

**** Included for the academic interest of the investigators

9.1.6. Analysis Plan

Abuse liability was assessed by comparing responses on 3 primary outcome variables:

Drug Liking: Responses to the question "Do you like the drug effect?" recorded on a 100mm VAS with anchor points labeled "not at all" and "extremely"

Positive Drug Effect: Responses to the question "Does the drug have any good effects?" also on a VAS.

MBG: Responses to the Morphine-Benzedrine Group (MBG) subscale of the Addiction Research Center Inventory (ARCI).

The protocol specified an analysis using a repeated measures ANOVA. This analysis focused on delineating the dose response of different flavors and doses of Nicorette compared to amphetamine by age.

9.1.7. Study Conduct

The study protocol was amended 7/25/97, 2/10/98, and 2/26/98. The basic design remained unchanged. Details of the analysis plan were requested and were submitted in the 2/26/98 amendment. Amendments were filed prior to breaking the study blind.

The following protocol deviations are noted by the sponsor:

One of the orders of drug administration in the 12x12 Latin square was not used and one was used twice (when the patient's weight was mistaken for an ID number.) Therefore subjects 120 and 123 received the same order of treatment.

Subject 015 received amphetamine followed by placebo original flavor Nicorette on 2 occasions rather than receiving mint placebo in one of the sessions. Mean data from all other subjects for the amphetamine mint placebo session were used for this subject.

Five of the women admitted to the study and randomized were not screened for pregnancy. They are being tracked to determine their pregnancy status.

Subject 007 misunderstood the Drug Effects Questionnaire Visual Analog Scale (marked a score of 50 rather than 0 to mean 'not at all'). Responses to this questionnaire were dropped from this subject's data. Other data from this subject were used in the analysis.

9.1.8. Patient Disposition

A total of 560 potential subjects were identified for this study. Of these, 119 subjects qualified for screening (105 could not be contacted, 312 did not qualify, 11 were not interested, and 13 were in the wrong age group.) Sixty of the 119 subjects did not show up for screening. Of 36 smokers aged 18 to 21, 20 were randomized to treatment (3 were ineligible based on medical history, 1 had a positive urinalysis, 10 had a CO<15ppm and 2 were not randomized). Of 23 subjects aged 22 to 50, 17 were randomized (1 was ineligible based on medical history, 3 had a CO<15ppm, and 2 were not randomized). Twelve (12) subjects in each age group completed the study. Among younger subjects there was 1 work conflict, 1 subject did not like the drug effect, 2 did not like the study, 2 were discharged for noncompliance and there were 2 no shows after randomization. Among older subjects, 2 had work conflicts, 2 did not like the study, and there was 1 medical discharge.

9.1.9. Demographics/Group Comparability

Demographics of completers and noncompleters are shown in the table below:

Table 5 Study Demographics: Completers and Dropouts

Characteristic	Completers N=24	Drop-outs N=13	P-value
Age	28 [11]	26 [8.7]	NS
Cigarettes per day	22 [5.4]	24 [7.4]	NS
% male	15 (63%)	7(54%)	NS
% white	14 (58%)	6 (46%)	NS
% educated to high or beyond	17(71%)	11 (85%)	NS

From table 11.2.1 of the sponsor's study report. Values are mean [SD], or N (%). P-values from Fisher's exact test or t-test as appropriate.

Table 6 Demographics of Completers by Age Group

Characteristic	Older Completers N=12	Younger Completers N=12	P-value
Age	37 [8.6]	19 [1.2]	N/A
Cigarettes per day	22 [6.5]	21 [4.1]	NS
% male	9 (75%)	6 (50%)	NS
% white	5 (42%)	9 (75%)	NS
% educated to high or beyond	8 (67%)	9 (75%)	NS

From table 11.2.1 of the sponsor's study report. Values are mean [SD], or N (%). P-values from Fisher's exact test or t-test as appropriate.

9.1.10.Dosing Information

See Design, above.

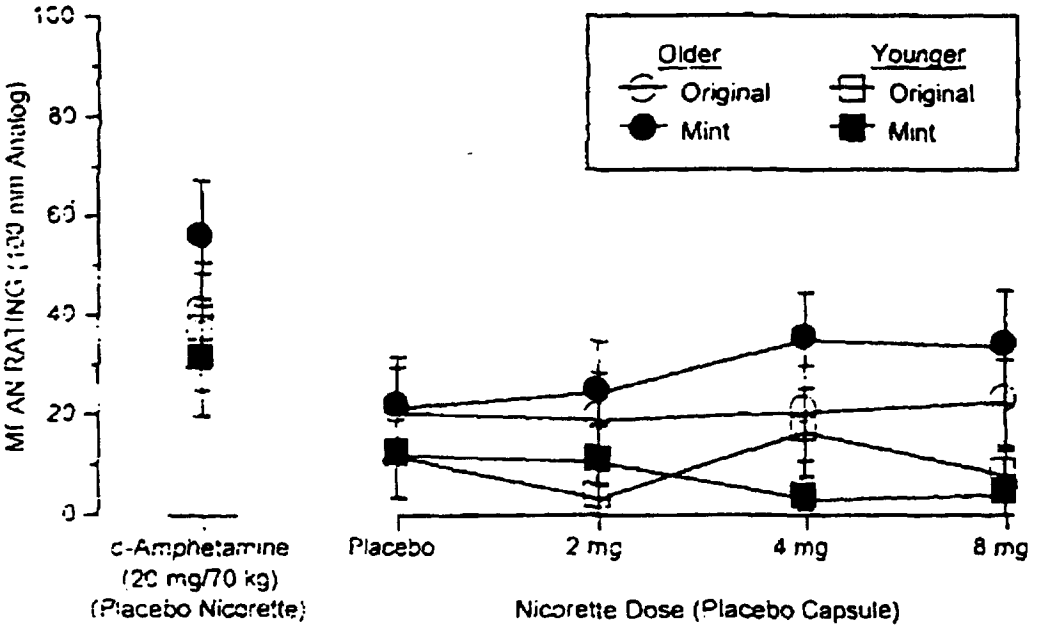
9.1.11.Results

9.1.11.1.Primary Outcome Variables (Sponsor's Analysis)

The following figures summarize the sponsor's analyses of the primary outcome variables in this study.

"Do You Like the Drug Effect?"

(Pharmacological Peak - Time 120)



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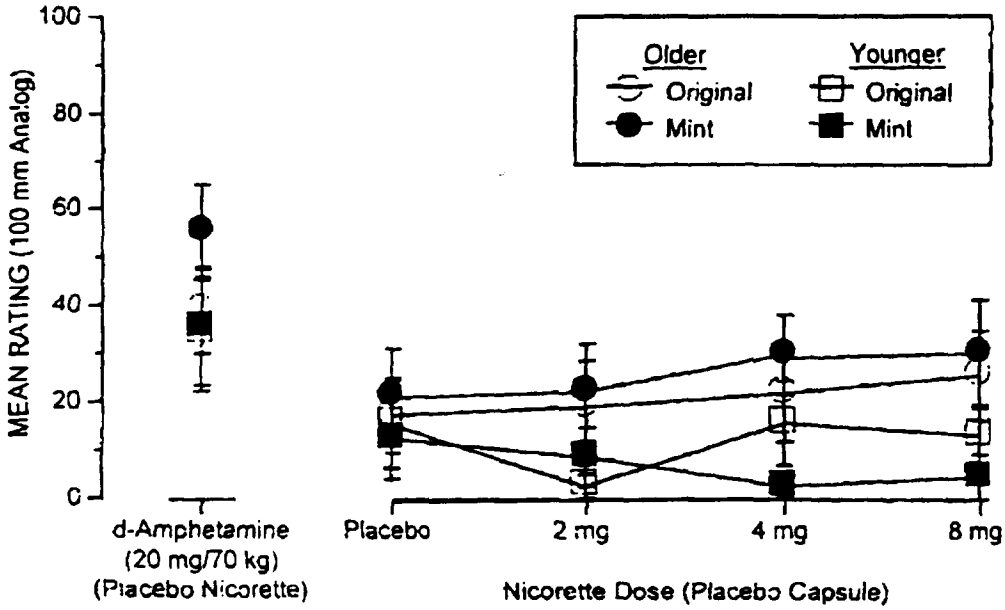
"Does the Drug have Any Good Effects?"

(Pharmacological Peak - Time 120)



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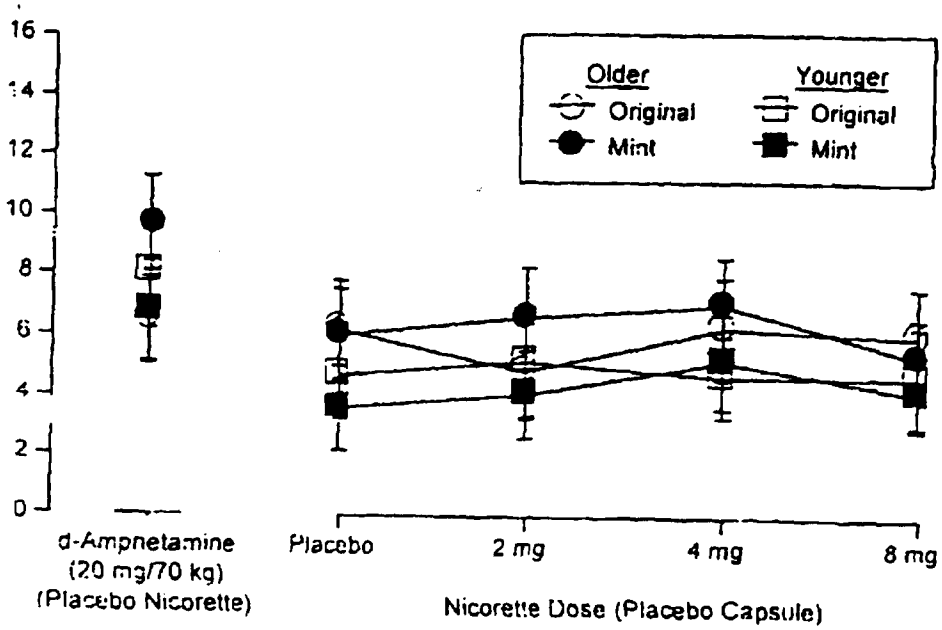
ARCI - MBG SCALE

(Pharmacological Peak - Time 120)



Y axis is mean response.

The sponsor's report notes that these results support the following conclusions:

1. The abuse liability of Mint Nicorette is low relative to d-amphetamine.
2. The abuse liability of Mint Flavor Nicorette is comparable to Original Flavor Nicorette
3. Younger subjects did not show evidence of higher potential for abuse of Mint Nicorette than older subjects.

The report also notes that subjects rated the Mint flavor as somewhat more palatable than the Original flavor, that scores on palatability measures remained low relative to confectionery gum, and that younger subjects did not find the gum more palatable than older subjects.

While the sponsor's conclusions may be statistically true, visual inspection of the above figures suggested that such an interpretation may be misleading. In particular, there appears to be high variability in individual responses, and there appeared to be some degree of overlap between responses to amphetamine and responses to Nicorette. To investigate this possibility, the reviewers conducted an individual subject analysis of selected outcome measures. This analysis is presented in the following sections.