CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-066/S010

MEDICAL REVIEW

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

MAY 31 2000

Applicant: SmithKline Beecham
NDA No: 18-612/SCF-028
20-066/SCF-010
Product: Orange Nicorette gum (Citrus Flavor) 2 mg
Orange Nicorette gum (Citrus Flavor) 4 mg
Submission: NDA Supplement dated February 21, 2000
Date Reviewed: March 2000
Date Completed: May 22, 2000

Introduction

SmithKline Beecham filed a chemistry supplement for the addition of citrus flavoring to their existing NDAs for Nicorette gum 2 and 4 mg. Nicorette gum, original flavor, 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 was approved for OTC marketing in the U.S. in December 1998. Orange (Citrus) Nicorette has never been marketed in the U.S., either as a prescription or OTC product. In support of the Orange Nicorette chemistry supplement, sponsor has provided a safety update.

Marketing

A. Worldwide

Orange Nicorette is currently approved in 18 countries for OTC marketing except for China where it is Rx. The product has been launched in 11 since June 1995. Due to marketing considerations, Orange Nicorette has not been launched in 7 countries. The sponsor stated that Orange Nicorette has not been withdrawn from any foreign market where it has been introduced. Table 1 lists the countries where Orange Nicorette 2 mg and 4 mg is currently available.

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

Country	Registration 2 mg and 4 mg	Launch 2 mg and 4 mg	Status
Sweden	4/95	6/95	See attachment for sponsor's clarification of marketing status: Rx or OTC
Norway	9/95	11/95	
Iceland	9/95	3/96	
Switzerland	10/95	3/96	
Denmark	12/95	3/96	
Finland	12/95	1/96	
England	3/96	Not launched	
Holland	5/96	9/96	
Canada	No approval needed	9/97	
Germany	2/96	1/97	
Ireland	7/96	12/96	
Austria	8/96	Not launched	
France	1/97	Not launched	
Greece	5/97	Not launched	
New Zealand	10/97	Not launched	
Australia	11/97	Not launched	
Belgium	9/97	Q4/97	
China	10/98	Not launched	

Sales information was provided for Sweden and Denmark only. Table 2 below shows the distribution in volume sales among the 3 formulations of Nicorette gum. In Sweden, sponsor reported that Orange Nicorette gum represented 5% of total Nicorette units sold in 1998. In Denmark, Orange Nicorette gum represented 22% of total Nicorette units sold in 1998.

Table 2: Total Nicorette Unit Sales Volume 1993 to 1998 (in thousands of boxes*)

	Sweden [Units, (%)]				Denmark [Units, (%)]			
	Total	Original	Mint	Orange	Total	Original	Mint	Orange
1993								
1994								
1995								
1996								
1997								
1998								

*from wholesaler to pharmacy

B. U.S.

In the U.S., Nicorette gum is available in the original and Mint flavours. As of July of 1998, (prior to Mint Nicorette sales), a total of [redacted] boxes have been sold, of which [redacted] 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 distinguish between original flavor and other flavors of gum, nor specifically between the 2 mg and 4 mg gum. 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, and when available, for Mint Nicorette as well.

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A. Deaths

A total of 5 fatal cases were reported in the September 28, 1998 submission for Mint Nicorette, and will not be repeated here. Table 3 summarizes 4 more fatal cases submitted to this chemistry supplement.

Table 3: Summary of Deaths

ID Number	Place	Date	Age	Sex	Event	Medical History	Comment
1998025476 2 mg		93?	64	M	Cardiac arrest and sudden death		No other information
1998025473 2 mg	UK	2/96	37	F	Found dead in bath. Had previously fainted while using gum.	Continued to smoke (40-50 cigs/day) while using gum and patches. Nicotine level c/w heavy smoker in blood	Fainting due to nicotine cannot be excluded; no other explanation at post-mortem
1998025480 2 mg	CAN	11/96	62	M	Cardiac arrest. Jaw muscle pain and arms hurting few weeks before death.	Irregular heartbeat, aortic stenosis. Smoked for 42 years. Started Nicorette (2mg) 5 weeks ago. Nicorette gum: 2 pieces/day	
1999019706 2 mg		6/99		M	Dropped dead after chewing one piece of Nicorette; per wife		No other information

Medical Officer's Comments:

A definitive conclusion that these deaths are drug related cannot be made on the basis of the information available. Where some information was provided, one patient had pre-existing cardiac disease, while the other continued to smoke heavily and used both gum and patch at the same time, although the post-mortem did not reveal any explanation for the death.

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15-Day Reports

Two cases of tongue cancer had previously been submitted and will be excluded from this table. All other cases of serious events (21 cases) that were previously submitted were also excluded. Table 4 is a listing of the remaining 15-day Reports for the 2 mg strength. Table 5 is a listing of the remaining 15-day Reports for the 4 mg strength.

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

Number	Date	Event
98022326	8/98	42 y.o. female used gum from 12/97 to 8/98. Had pain in R arm and upper back; required coronary bypass. H/o of hypercholesterolemia.
98024833	1/97	48 y.o. female, had 3 episodes of panic attacks. Quit smoking and started gum (6-8 pieces/day) 3 days earlier. H/o depression.
98024971		From UK. 41 y.o. female used gum 3/92 to 3/93. Underwent excision of oral leukoplakia. H/o hypertension, tachycardia.
98025443		From Canada. Female reported chemical reaction and hospitalized X 1 week after using gum. Physician clarified patient was admitted for psychotic breakdown. H/o bipolar disorder and hypertension.
99001647	11/98	51 y.o. male used gum for 2-3 years, 10-20 pieces/day. Diagnosed with malignant fibrous histiocytoma sarcoma in retroperitoneal area in 11/98. Stopped gum use prior to diagnosis.
99004317	11/98	45 y.o. male used gum without following directions; used too much, chewed constantly and did not taper. Experienced tingling in face and chest, flushed face, claustrophobia and fear of the dark. Similar sx in 97 (also using gum then), negative workup in hospital. H/o anxiety attacks, mood disorders, depression, headaches and eye problems.
99006937		77 y.o. female who reported that she had been using gum since it was available Rx, on her oncologist's recommendation. She also reported that she has lung cancer.
99008429	4/99	68 y.o. female using gum for 8 years. Son reported hospitalization for pneumonia.
99008996	12/99	65 y.o. female reported her hair is falling out. Had been using gum for >1 year. Hospitalized in 9/97 for arrhythmia.
99009043	11/98	Foreign report. 56 y.o. male started gum 11/04 to 11/26, stomach discomfort with each dose. Surgery 11/12 for anal fistula, treated with stypic, analgesics and antibiotics. 11/27 vomited large amount black matter. BP 79/39, with hematemesis. Treated with fluids, H2 blocker and stypic. 11/30 endoscopy revealed gastric ulcer. 3/98 endoscopy revealed atrophic gastritis. Meds: Cefcapene Pivoxil HCl, Teprrenone, Tranexamic Acid, Disopain/Mefesoiac, Tosufloxacin Tosilate, Loxonin, Voltaren.
99009979	4/99	From France. 60 y.o. male using gum X 10 years, 96 pieces/day. Hospitalized for acute unilateral auditory acuity loss with tinnitus.
99014777	6/99	43 y.o. female started using gum 5/5 to 6/18. Sweating, N&V on 6/17. Admitted to ER 6/18 for pain in shoulder, chest tightness, HR >180, and glucose 339. Diagnosed with DM Type II.
99017904	5/99	From clinical trial. 34 y.o. female in 2 mg arm, took gum 4/20 to 5/2. Hospitalized 5/4 to 5/7 for elevated liver enzymes, etiology unknown. Treated with Phenergan and Demerol. Investigator stated possibly related to study drug.
99027447	6/98	64 y.o. male used gum since 11/96, 4-5 pieces/day. Reported MI x 2 in 5/99. H/o aortic aneurysm, bilateral femoral-ileal surgery, diabetes.

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

Number	Date	Event
98027683	11/98	62 y.o. female with 30 yr hx of smoking 1.5 packs/day, COPD. Used 3 pieces of gum/day + 10 cigs in evening X 3 weeks. Treated in ER for difficulty breathing; d/c'd with inhaler. Admitted next am for 4 days, treated for bronchitis. MD advised continued use of gum for smoking cessation.
99012116	5/99	64 y.o. male from clinical trial, in 4 mg gum treatment arm. Rec'd study meds between 4/2 to 4/4. C/o nausea, stomach pains with lower chest pain since 4/18. Admitted for cholecystectomy 5/13 for acute acalculus cholecystitis; possibly drug related per investigator. Pre-op w/u revealed lung ca metastatic to adrenal gland. H/o chronic bronchitis.
99012143	5/99	70 y.o. female from clinical trial, began using product (active or placebo) 3/25, about 15 pieces/day. Had chills 5/8. Admitted 5/9 to 5/14 for pneumonia; possibly drug related per investigator.
99013349	5/99	54 y.o. female from clinical trial, began using product (active or placebo) 4/2. Admitted 5/26 for pneumonia; possibly drug related per investigator. H/o COPD.
99013352	5/99	49 y.o. male from clinical trial, in 4 mg gum treatment arm. Rec'd study meds beginning 5/12. Hospitalized 5/29 for motorcycle accident trauma.
99024575		From Sweden: 62 y.o. with 'smoker lungs', smoked 40-50 cigs/day X 40 years. Used gum last 5 years (stopped smoking). Had 3 episodes of swelling tongue, requiring hospitalization X 24 hours each time. Used gum in between.

Medical Officer's Comments:

15-Day Reports were submitted for the 2 mg gum, and for the 4 mg gum. After exclusion of the fatal cases and cases already submitted to the Mint supplement, Table 4 lists 14 cases for the 2 mg gum and Table 5 lists 6 cases for the 4 mg gum. Among the cases reported for the 2 mg strength, there is one case of severe GI bleed, but there was a history of atrophic gastritis, stress from recent surgical procedures and use of various analgesics. There is one case of elevated liver enzymes without obvious etiology in a subject taking 2 mg Nicorette in a clinical trial. The investigator classified this case as possibly related to the study drug.

Among the cases reported for the 4 mg strength, 4 cases had respiratory system involvement (2 bronchitis, 2 pneumonia); 1 had repeated episodes of swelling of the tongue, and 1 was involved in a motorcycle accident. Four of the 6 cases were from subjects in a double blind placebo-controlled trial (Smoking Cessation by Gradual Reduction). Of these 4, 3 subjects who were older (54 to 70 years old) were treated for respiratory illnesses (bronchitis, pneumonia). The study investigator had noted that these cases could possibly be related to the drug; however, it should be pointed out that these subjects may have had other reasons for having respiratory illnesses. The 4th clinical trial subject was hospitalized for problems secondary to a motorcycle accident.

Long-term use was noted in 8 of the 15-Day Reports (up to 8 years) for the 2 mg strength and in 1 report for the 4 mg strength (5 years). One patient had been using the gum, on the recommendation of her oncologist, since its availability as a prescription drug. One case from the UK is notable for use of the gum for about a year and the development of oral leukoplakia requiring excision. One case from Sweden is notable for swelling of the tongue.

It is difficult to attribute drug causality in most of these cases. There may have been underlying medical conditions such as psychiatric disorders, and atherosclerotic disease that may have contributed to the reported conditions.

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 October 31, 1999.

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	4	Autonomic Nervous System	1
Body as a Whole General	22	Body as a Whole General	27
Cardiovascular General	5	Cardiovascular General	7
Central & Peripheral Nervous System	23	Central & Peripheral Nervous System	12
Collagen	2		
Endocrine	1		
Gastrointestinal System	41	Gastrointestinal System	37
Hearing and Vestibular System	4		
Heart Rate & Rhythm	3	Heart Rate & Rhythm	11
Liver & Biliary	1	Liver & Biliary	1
Metabolism & Nutrition	1	Metabolism & Nutrition	2
Musculoskeletal	3	Musculoskeletal	2
	2	Myocardium Endocardium Pericardium Valvular	3
Neoplasm	1	Neoplasm	5
Psychiatric	16	Psychiatric	10
Reproductive Female	2		
Reproductive Male	1		
Resistance Mechanism	1	Resistance Mechanism	1
Respiratory System	20	Respiratory System	16
Skin And Appendages	17	Skin And Appendages	7
Special Senses Other	2		
Vision	2		
		WBC And Reticuloendothelial System	2
Unmapped Terms	8	Unmapped Terms	6
Total	176	**Total**	150

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 about 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, vomiting, stomach ache, stomatitis, tooth disorder, gingival bleeding, mouth ulceration), Body as a Whole (such as pain, face edema, malaise, injury, lack of efficacy), Central and Peripheral Nervous System (such as paresthesia circumoral, paresthesia,

headache), Psychiatric (such as drug dependence), Respiratory system (such as throat sore, pharyngitis), and Skin and Appendages (such as blisters, rash).

Table 7: ADEs by Body Systems reported by Consumers (4/1/96 to 10/31/99)

Consumer: 2 mg			Consumer: 4 mg		
BODY SYSTEM	**Orig**	**Mint**	**BODY SYSTEM**	**Orig**	**Mint**
			Application Site	2	
Autonomic Nervous System	76	8	Autonomic Nervous System	91	9
Body as a Whole General	505	35	Body as a Whole General	562	56
Cardiovascular General	44	4	Cardiovascular General	46	2
Central & Peripheral Nervous System	833	50	Central & Peripheral Nervous System	890	52
Endocrine	2				
Gastrointestinal System	2831	156	Gastrointestinal System	3215	190
Hearing And Vestibular	14	2	Hearing And Vestibular	15	2
Heart Rate Rhythm	175	13	Heart Rate Rhythm	120	10
Liver & Biliary	2		Liver & Biliary	3	1
Metabolism & Nutrition	53	1	Metabolism & Nutrition	52	7
Musculoskeletal	46	2	Musculoskeletal	38	1
Myocardium Endocardium Pericardium Valvular	6				
Neoplasm	13		Neoplasm	2	
			Platelet Bleeding Clotting	1	1
Psychiatric	1481	31	Psychiatric	823	31
RBC		1			
Reproductive Female	3	2			
Reproductive Male	10		Reproductive Male	4	
Resistance Mechanism	13	1	Resistance Mechanism	10	
Respiratory System	553	38	Respiratory System	548	32
Skin And Appendages	299	17	Skin And Appendages	296	27
Special Senses Other	38	2	Special Senses Other	47	1
Urinary System	13		Urinary System	22	
Vascular Extracardial	7		Vascular Extracardial	6	
Vision	29	3	Vision	19	
WBC And Reticuloendothelial System	7		WBC And Reticuloendothelial System	3	
Unmapped Terms	57	7	Unmapped Terms	54	3
Total	7110	373	**Total**	6869	425

Medical Officer's Comments:

Table 8 is a compilation of the ADEs most frequently reported by consumers for both dosage strengths.

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

Body System	Included Term (events >30)
Body as a Whole **2 mg: 505 + 35** **4 mg: 562 + 56**	Chest pain, Lack of Efficacy, Pain
	Included Term (events >50)
GI System **2 mg: 2831 +156** **4 mg: 3215 + 190**	Diarrhea, Gingivitis, Heartburn, Hiccup, Mouth Irritation, Mouth Ulceration, Nausea, Stomach Ache, , Stomach Upset, Stomatitis, Tongue Pain, Vomiting
	Included Term (events >30)
CNS & PNS **2 mg: 833 + 50** **4 mg: 890 + 52**	Burning skin, Dizziness, Headache, Light-headed Feeling, Numbness Localized, Paresthesia Circumoral, Spasm Oropharyngeal
	Included Term (events >20)
Psychiatric **2 mg: 1481 + 31** **4 mg: 823 + 31**	Anxiety, Drug Dependence (2 mg:1227, 4 mg:601), Irritability, Nervousness
	Included Term (events>30)
Respiratory **2 mg: 553 +38** **4 mg: 548 + 32**	Breathing Difficulty, Coughing, Pharyngitis, Throat Sore
	Included Term (events>20)
Skin & Appendages **2mg: 299 + 17** **4 mg: 234**	Blisters, Hives, Itching, Rash

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 consumer reports of drug dependence[1] (2 mg: 1227, 4 mg: 601) as well as health care professional reports of drug dependence (2 mg: 14, 4 mg: 4). 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

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1 The sponsor's definitions of the coded terms (from Mint Supplement) 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.

consumers are switching addictions from cigarettes to Nicorette gum, or even using both at the same time. Twenty-four counts of drug addiction/addiction any drug (2 mg: 20, 4 mg: 4) were also reported by consumers. There were no reports coded as drug addiction/addiction any drug from health care professionals.

D. Worldwide Adverse Events

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	7	1,252,800
Switzerland	4	873,200
New Zealand	4	209,200
Australia	38	2,481,600
Germany	0	681,600
Norway	1	619,600
Sweden	13	3,988,800
Denmark	2	1,111,200
Great Britain	37	3,919,600
France	10	578,000
Belgium	1	316,600
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 Great Britain, there were 4 reports 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 adverse events. The number of reports was received for varying time periods in each country, ranging from 3 to 11 years. It is unclear how the numbers of treated patients were derived. In general, the reported ADEs were known and expected for Nicorette, and the pattern of distribution for the ADEs by body system, was as expected.

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 December 1999, 13 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 for the three year period since introduction of OTC Nicorette gum.

A. Media Tracking

The sponsor used the Porter/Novelli agency to monitor the press. Approximately 1600 separate media items were identified. The majority of reports were about the detrimental health effects of tobacco products and the availability of new treatments for smoking cessation. There were 9 reports related to underage smoking but no reports of underage abuse of nicotine replacement products.

B. Consumer Tracking

The sponsor has been tracking consumers via the toll-free telephone number listed on product packaging. There have been a total of approximately 52,500. The overwhelming majority of these calls were about consumer complaints and questions about Nicorette. The majority of complaints were about non-serious adverse experiences. The majority of questions were about procedures for proper use. A total of 52 calls (0.1% of all calls) inquired about the appropriateness of Nicorette use for those under the age of 18.

The sponsor has also undertaken an on-going telephone survey via Cooper Research, Inc. of current and former smokers. A total of 14,500 households have been contacted. A total of 5 reports of underage use (0.03% of entire population sampled) have been identified. The sponsor believes that no identifiable trends regarding the patterns of misuse/abuse by adolescents exist.

C. Theft Surveillance

According to the sponsor, salesforce representatives are in constant contact with retail trade accounts to solicit information concerning pilferage. Products are made available only to accounts that can adequately verify the age of purchasers. Nicorette is not distributed to convenience stores or vending machines. Retail accounts are encouraged to stock Nicorette with other OTC medications and are reminded to verify the age of purchasers. The sponsor has also provided on request, lockable merchandising racks designed to minimize the theft potential. Since the availability of Nicorette gum OTC, no significant reports of theft have been received.

D. Committed Quitters Program (CQP)

Consumers can enroll in the CQP by telephone. Total enrollment was recorded at 142,500. Approximately 0.3% (430 callers) were under 18 years of age. Callers under 18 years old are advised to discuss product use with their physicians. No confirmations of actual product use by adolescent callers have been made. The context of some of these calls by adolescents may have been to inquire about a smoking cessation program.

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)

Two SDFSC Surveys have been conducted by [redacted], for the sponsor. The surveys were conducted between 10/96 and 2/97 and again between 10/98 and 1/99. Interviews

were completed with 1,063 SDFSC and 749 community members referred by the SDFSCs. Approximately 2.0% ('97) and 2.5% ('99) of interviewees volunteered any awareness of nicotine patch or gum abuse. When prompted about NRT products, these percentages increased to 4.5% ('97) and 5.8% ('99) of all respondents. The majority of respondents, 79% ('97) and 76% ('99), reported they felt that the abusers were current tobacco users and that most cases involved smokers using NRT products during times when they were unable to smoke. Respondents felt that adolescents using NRT products for smoking cessation increased from 8.3% ('97) to 18.9% ('99). Overall, respondents were much more likely to be aware of abuse of other OTC drugs (diet medication, non-medicinal inhalants, stay-alert medications, cough syrups, and antihistamines) than NRT products.

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 were indicative of abuse/misuse of NRT products, and Nicorette specifically, by those less than 18 years of age, but it may be difficult for these surveillance efforts to pick up small localized outbreaks. 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, ove. [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 have been sold ('93-'98) in Sweden and Denmark (Table 2 above). Mint sales in the U.S. were not reported in this update. Nicorette Orange is marketed in 11 countries outside of the U.S., since 1995.

The safety profile from postmarketing experience reveals a low rate of adverse events relative 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 9 deaths were reported worldwide since Rx marketing. It is reasonable to conclude that in at least 5 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. 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 naive, underage adolescents, by the addition of mint flavoring which may make the gum more palatable. Postmarketing surveillance efforts by the sponsor has not revealed much use/misuse/abuse by underage adolescents. However, these efforts should be continued for Nicorette Orange as well, since the information on the U.S. marketing of Mint Nicorette covers only a short time period.

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. 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. 5/30/00
Medical Officer
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/S/

Linda M. Katz, M.D., M.P.H. 5/31/00
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Attachment

Orange flavor Nicorette® gum is currently approved in the 18 countries listed in the table below.

Table 3.3.1-A Foreign Market Status of Citrus (Orange) Flavor Nicorette® Gum

Country	Registration Year		Rx or OTC	Date Launched
	2 mg	4 mg		
Sweden	April 1995	April 1995	OTC[1]	June 1995
Norway	September 1995	September 1995	OTC[2]	November 1995
Iceland	September 1995	September 1995	OTC[3]	March 1996
Switzerland	October 1995	October 1995	OTC (30 count)[3]	March 1996
Denmark	December 1995	December 1995	OTC[3]	March 1996
Finland	December 1995	December 1995	OTC[3]	January 1996
England	March 1996	March 1996	OTC (2mg)[4] (4mg)[3]	Not Launched
Holland	May 1996	May 1996	OTC[3]	September 1996
Canada	No Approval Needed		OTC[3] (4 mg Rx)	September 1997
Germany	February 1996	February 1996	OTC[3] (4 mg Rx)	January 1997
Ireland	July 1996	July 1996	OTC[3]	December 1996
Austria	August 1996	August 1996	OTC[3]	Not Launched
France	January 1997	January 1997	OTC[3] (4mg Rx)	Not Launched
Greece	May 1997	May 1997	OTC[3] (4mg Rx)	Not Launched
New Zealand	October 1997	October 1997	OTC[1]	Not Launched
Australia	November 1997	November 1997	OTC[3]	Not Launched
Belgium	September 1997	September 1997	OTC[3]	Q4 1997
China	October 1998	October 1998	Rx	Not Launched

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[1] **Pharmacy only - Self Service**

Consumers can purchase products only in a pharmacy. The product is shelved in the open section of the store and can be selected and purchased without contact/interaction with pharmacist.

[2] **Pharmacy Only - Discretionary Self Service**

Consumers can purchase products only in a pharmacy. The pharmacy owner can decide whether to place product for self service or behind the counter.

[3] **Pharmacy Only - No Self Service**

Consumers can purchase products only in a pharmacy. Product shelved behind the counter requiring pharmacist contact/interaction for purchase.

[4] **General Sales License**

Consumers can purchase products in and outside of pharmacy. The product is shelved in open section of store allowing self selection and purchase.

CC:
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