Public Assessment Report

National Procedure

Nicorette Fruitfusion 6mg Gum
PL 15513/0381

Nicotine resinate

McNeil Products Limited

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Nicorette Fruitfusion 6mg Gum (PL 15513/0381). It explains how Nicorette Fruitfusion 6mg Gum was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Nicorette Fruitfusion 6mg Gum, patients should read the Package Leaflet or contact their doctor or pharmacist.

What is Nicorette Fruitfusion 6mg Gum and what is it used for?
Nicorette Fruitfusion 6mg Gum is a nicotine replacement therapy for heavy smokers. It is intended for use in adults and children over 12 years. It is used to relieve and/or prevent withdrawal symptoms and reduce the cravings for nicotine that you get when you try to stop smoking, or when cutting down the number of cigarettes you smoke. Nicorette Fruitfusion 6mg Gum can also be used when you are pregnant or breast-feeding to help you stop smoking, as the risks to your baby are far less than if you continue to smoke.

The higher strength, 6mg gum has been approved for supply as a General Sales Medicine (GSL) following a reclassification application which demonstrated that the safety of the product was suitable for supply without the supervision of a pharmacist.

How does Nicorette Fruitfusion 6mg Gum work?
Nicorette Fruitfusion 6mg Gum contains the active substance nicotine (as nicotine resinate).

When you stop smoking, or cut down the number of cigarettes you smoke, your body misses the nicotine that you have been absorbing. You may experience unpleasant feelings and a strong desire to smoke (craving). This indicates that you were dependent on nicotine.

When you chew Nicorette Fruitfusion 6mg Gum, nicotine is released and passes into your body through the lining of your mouth. The nicotine released from the gum is sufficient to relieve the unpleasant withdrawal symptoms. It will also help to stop the craving to smoke, but Nicorette Fruitfusion 6mg Gum will not give you the "buzz'' you get from smoking a cigarette.

How is Nicorette Fruitfusion 6mg Gum used?
The number of Nicorette Fruitfusion 6mg Gum you use each day will depend on how many cigarettes you smoked and how strong they are. See the below dosing table to find out the dose you should take.

Number of cigarettes you smoke per day	Dose of Gums
20 cigarettes or fewer	One 2 mg gum as required to relieve cravings.
More than 20 cigarettes as required to relieve cravings	One 4 mg gum as required to relieve cravings.
More than 20 cigarettes requiring strong craving relief	One 6 mg gum as required to provide enhanced craving relief (i.e. decrease in craving intensity, faster craving relief or longer craving relief) when compared to the 4mg gum

Use only one piece of gum at a time. Do not use more than 15 gums per day. The frequency with which you use the gums will depend on how many cigarettes you smoked and how strong they were. Children aged between 12 to 18 years, should consult with a doctor, nurse or pharmacist before starting to use this product. The method of chewing Nicorette Fruitfusion 6mg Gum is not the same as for ordinary chewing gum. Nicorette Fruitfusion 6mg Gum is chewed to release nicotine then rested so that nicotine can be taken in through the lining of the mouth. If Nicorette Fruitfusion 6mg Gum is chewed continuously, the nicotine is released too quickly and is swallowed. This may irritate your throat, upset your stomach or give you hiccups. For more information on chewing this product, please consult the Patient Information Leaflet.

How has Nicorette Fruitfusion 6mg Gum been studied?
Nicorette Fruitfusion 6mg Gum is a "line-extension" of the existing medicines Nicorette Fruitfusion 2mg and 4mg Gum. In support of this application, pharmacokinetic data from three studies were submitted, comparing Nicorette Fruitfusion 6mg Gum with other products, and pharmacodynamics data from two studies were submitted, to measure the 6mg dose effect on cravings.

What are the possible side effects of Nicorette Fruitfusion 6mg Gum?
Because Nicorette Fruitfusion 6mg Gum is a "line extension" of the existing medicines Nicorette Fruitfusion 2mg and 4mg Gum, its benefits and possible side-effects are taken as being the same.

For further information, please see Section 4 the Package Leaflet.

Why is Nicorette Fruitfusion 6mg Gum approved?
It was concluded that Nicorette Fruitfusion 6mg Gum has a positive benefit-risk profile to allow it to be used for heavy smokers (>20 cigarettes a day).

What measures are being taken to ensure the safe and effective use of Nicorette Fruitfusion 6mg Gum?
A risk management plan (RMP) has been developed to ensure that Nicorette Fruitfusion 6mg Gum is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Nicorette Fruitfusion 6mg Gum, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Nicorette Fruitfusion 6mg Gum
The UK first granted a marketing authorisation for this product on 16 October 2013.

The full PAR for Nicorette Fruitfusion 6mg Gum follows this summary and includes an annex which contains the assessment of the reclassification to a GSL product.

For more information about treatment Nicorette Fruitfusion 6mg Gum, read the Package Leaflet or contact your doctor or pharmacist.

This summary was last updated in February 2016.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted McNeil Products Limited a marketing authorisation for Nicorette Fruitfusion 6mg Gum (PL 15513/0381) on 16 October 2013.

This product is a General Sales List (GSL) medicine that relieves and/or prevents craving and nicotine withdrawal symptoms associated with tobacco dependence in highly dependent smokers (> 20 cigarettes per day). It is also indicated to aid smokers wishing to quit or reduce prior to quitting, to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them. Nicorette Fruitfusion 6mg Gum is indicated in pregnant and lactating women making a quit attempt.

This product contains the active substance nicotine resinate. Nicotine is a liquid alkaloid obtained from the dried leaves of the tobacco plant, Nicotiana tabacum and related species (Solanaceae). Tobacco leaves contain 0.5 to 8% of nicotine combined as malate or citrate.

Nicotine is readily absorbed through mucous membranes and the skin; bioavailability of oral nicotine is low due to extensive first pass metabolism. Nicotine is widely distributed; it crosses the blood brain barrier and the placenta and is found in breast milk. The elimination half-life is about 1 to 2 hours. Nicotine is metabolised mainly in the liver via the cytochrome P450 isoenzyme CYP2A6 to cotine and nicotine-N-oxide. Nicotine and its metabolites are excreted in the urine.

This application was made as a national application, under Article 8(3) of Directive 2001/83/EC, as amended, for a line-extension to the existing products Nicorette Fruitfusion 2mg and 4mg gum (PL 15513/0136 & 0137).

As the pharmacological, pharmacokinetic and toxicological properties of nicotine have been well-characterised, no new non-clinical studies were submitted and none were required.

In support of this application, pharmacokinetic data from three studies were submitted, comparing Nicorette Fruitfusion 6mg Gum with other products, and pharmacodynamics data from two studies were submitted, to measure the 6mg dose effect on cravings. All clinical studies were conducted in-line with current Good Clinical Practice.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the MHRA has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the MHRA has accepted copies of current GMP Certificates of satisfactory inspection summary reports, as certification that acceptable standards of GMP are in place at those non-Community sites.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A marketing authorisation was granted for this product on 16 October 2013. A reclassification application was also granted for this product to change its legal status from a

Pharmacy-only (P) to a General Sales List (GSL) product. An assessment of the reclassification application is provided as an annex to this report.

II QUALITY ASPECTS

II.1 Introduction

This application was made as a national application, under Article 8(3) of Directive 2001/83/EC, as amended, for a line-extension to the existing products Nicorette Fruitfusion 2gm and 4mg gum (PL 15513/0136 & 0137). A quality overall summary has been prepared by an appropriately qualified person and a suitable summary of the quality data that have been submitted.

Nicorette Fruitfusion 6mg Gum is a square, coated and whitish coloured piece of medicated chewing gum. Each piece of gum contains 6mg nicotine, as nicotine resinate. As well as the active substance, nicotine resinate, this product contains the following excipients:

- Core gum - Chewing gum base (contains butylated hydroxy toluene (E321)), xylitol (E967), peppermint oil, anhydrous sodium carbonate (E500), acesulfame potassium (E950), levomenthol and light magnesium oxide (E530).
- Sub-coating – Tuttifrutti flavour, hypromellose (E464), sucralose (E955), polysorbate 80 (E433).
- Coating – xylitol (E967), acacia, titanium dioxide, Tuttifrutti flavour, carnauba wax (E903).

The product is packaged in:

- polyvinylchloride/polyvinylidene chloride/aluminium blisters, each containing 15 pieces of gum, which are boxed in laminated cardboard packs of 105 and 210 pieces.
- laminated cardboard boxes wrapped in transparent plastic film containing 25 pieces of gum, supplied in packs of 25, 100 (4 x 25) and 200 (8 x 25) pieces.

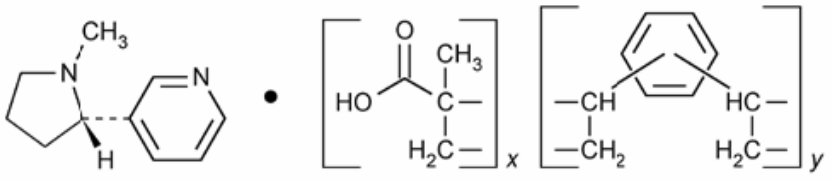
Not all pack sizes may be marketed.

II.2 DRUG SUBSTANCE

rINN: Nicotine resinate

Chemical Name: Nicotine resinate

Structure:



Molecular Formula: $C_{10}H_{14}N_2 (C_4H_6O_2)_x (C_{10}H_{10})_y$

Molecular Weight: 162 + 86(x) + 130(y)

Appearance: A white or slightly yellowish powder, hygroscopic
Solubility: Practically insoluble in water.

A European Pharmacopoeia monograph is available for nicotine resinate.

All aspects of the manufacture and control of nicotine resinate is covered by a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

The objective of the pharmaceutical development was to produce a safe, tolerable gum containing 6mg nicotine (as nicotine resinate) that could be considered a line-extension of the existing product licences for Nicorette Fruitfusion 2mg and 4mg gum (PL 15513/0136 & 0137).

With the exception of the gum base and the Tuttifrutti flavouring, all excipients comply with their respective European Pharmacopoeia monographs. The gum base and the Tuttifrutti flavouring comply with suitable in-house specifications.

Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of human or animal origin are used in the final product.

None of the excipients are sourced from genetically modified organisms.

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification

The finished product specification is satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished products stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years for both the blister packs and the box (unopened) is accepted. The box should be used within 3 months of opening.

The storage conditions are “This medicinal product does not require any special temperature storage conditions. Store in original container to protect from light” for the blister packs and box.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended from a pharmaceutical perspective.

III NON-CLINICAL ASPECTS

With the exception of non-clinical data submitted to study the impurities present in the active substance and drug product, no new non-clinical data were submitted and none were required. A non-clinical overview has been prepared by an appropriately qualified person and is a suitable summary of the non-clinical aspects of this application.

An Environmental Risk Assessment (ERA) has been submitted, providing calculations for the Predicted Environmental Concentration in surface water ($PEC_{surface\ water}$) and also a

Persistent Bioaccumulative and Toxic (PBT) assessment. Results from a Phase II Tier A analysis have also been provided. Based on this, the special precautions for disposal in section 6.6 of the Summary of Product Characteristics (SmPC) are "Dispose of Nicorette Gum sensibly. Any unused product or waste material should be disposed of in accordance with local requirements." This is acceptable.

No new non-clinical concerns were raised from the data submitted for the impurities and the excipients. All limits for active substance and finished product impurities are acceptable, and in-line with current guidance. All excipient levels comply with current regulations.

Conclusions

The grant of a marketing authorisation is recommended from a non-clinical perspective.

IV CLINICAL ASPECTS

IV.1 Introduction

With the exception of the below studies, no new clinical data have been submitted for these applications. A clinical overview has been written by an appropriately qualified person and is a suitable summary of the pharmacokinetics (PK), pharmacodynamics (PD), efficacy and safety of this product.

IV. 2 Pharmacokinetics

The following studies were submitted in support of this application:

Type of Study	Study Identifier	Location (No. of centers) Study dates	Primary Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Included/ Completed (Planned)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report Location in Module 5
PK	NICTDP1070	Lund, Sweden (1) May – June 2008	To compare the NMG* 6 mg vs. reference products regarding single-dose PK parameters.	Randomized, single-dose (Part I) and multiple-dose (Part 2), crossover. Controls: nicotine gums	NMG* 6 mg, 1 gum, BA NicoretteGum 2 mg, 1 gum, BA NicoretteGum 4 mg, 1 gum, BA	24/23 (24)	Healthy male or female smokers	Part 1: 10 h/visit. Two single-doses (eigth hours apart), three treatment visits. Part 2: 7 h/visit. Multiple-dose, two treatment visits.	Completed; Full CSR 5.3.3.1.1
PK	NICTDP1080	Lund, Sweden (1) Oct – Nov 2010	Comparison of MNG 6 mg vs. reference products regarding single-dose PK parameters.	Randomized, single-dose, crossover. Controls: nicotine gums and lozenge	NMG 6 mg, 1 gum, BA NicoretteGum 2 mg, 1 gum, BA Nicorette Gum 4 mg, 1 gum, BA Nicotine Lozenge 4mg, 1 lozenge, BA	44/42 (44)	Healthy male or female smokers	Single-dose, 12h/visit, four treatment visits.	Completed; Full CSR 5.3.3.1.2
PK	NICTDP1081	Lund, Sweden (1) Feb – May 2011	To compare steady-state nicotine PK parameters of NMG 6 mg treatments with reference products.	Randomized, multiple-dose, crossover. Controls: nicotine gum and lozenge	NMG 6 mg, 12x1 gum/ h, BA NMG 6 mg, 8x1 gum/ 90 min, BA Nicorette Gum 4 mg, 12x1 gum/h, BA Nicorette Gum 4 mg, 8x1 gum/90 min, BA Nicotine Lozenge 4mg, 12x1 lozenge/h, BA	50/39 (50)	Healthy male or female smokers	Multiple-dose, 12 h/visit, five treatment visits.	Completed; Full CSR 5.3.3.1.3

Abbreviations: PK=pharmacokinetics; BA=buccal administration
*NMG in Study NICTDP1070 was denominated as Nicorette® Freshfruit® 6 mg gum

Study NICTDP1070

The study was divided into two parts. In Part I (visits 1, 2, and 3), each 10-hour treatment visit consisted of a single morning dose of nicotine, an 8-hour nicotine free interval with blood sampling, and a second single nicotine dose. The second dose (treatment randomised separately) was given to allow a preliminary evaluation of treatment effects on craving in the study sample after witnessed nicotine abstinence and without potential disturbances by blood sampling procedures and questions. A crossover design was chosen for this study allowing a within-subject comparison between the study products.

The investigational products were given in randomised order, and included Nicorette Freshfruit® 6 mg gum (Nicorette Fruitfusion 6mg Gum), and Nicorette Freshfruit® 2 mg and 4 mg gum.

Each morning in Part I of the study (Treatments A, B and C), following a 12-hour nicotine abstinence period, subjects received their first trial medication. They were instructed to place the gum on the tongue and chew it once every 2 seconds for 30 minutes; a metronome was used to control the chewing rate. Subjects were also instructed to swallow saliva once every minute. Talking was not allowed during the chewing period. After eight hours, subjects received their second trial medication for the day. The same instructions for chewing and swallowing as during the first administration were valid and no talking was allowed.

During Part II of the study (Treatments D and E) the subjects were instructed to chew one gum every second hour for 2.5, 5, 10, or 20 minutes. The same instructions for chewing and swallowing as during Part I of the study was given, and no talking was allowed.

After the single morning dose, blood was sampled for PK analysis, irritation in mouth and throat, urges to smoke, acceptability, interest in product and palatability were assessed. The gums were collected for analysis of residual nicotine.

Subjects were also monitored to capture any adverse events that occurred. Time without Nicotine Replacement Therapy (NRT), each lasting for at least 36 hours, separated the treatment visits.

Blood sampling was performed pre-dose and 5, 10, 15, 20, 30, 45, and 60 minutes, as well as 1.25, 1.5, 2, 3, 4, 6, 8 and 10 hours after administration.

Used chewing gums were collected and analysed using a validated high-pressure liquid chromatography (HPLC) method.

Irritation experienced in the mouth and throat was rated before and 5, 15, 30, and 60 minutes after administration of the morning dose. Palatability was rated on a 100 mm Visual Analog Scale (VAS), 10 and 30 minutes after administration of the morning dose. Acceptability was rated on a 9-grade scale, 10 and 30 minutes after administration of the morning dose. Interest in product was rated on a 5-grade scale, 10 and 30 minutes after administration of the morning dose. Urges to smoke were rated and recorded before and 1, 2, 3, 4, 5, 6, 7, and 8 hours after the morning administration using a 100 mm VAS. Furthermore, ratings were made 2.5, 5, 10, 15, 20, 30 45, 60, 90, and 120 minutes after the evening dose.

Treatments in Part I of the Study

Treatment	Drug	Form	Route	Nicotine Dose	Regimen	#Subjects
A	Nicorette® Freshfruit®	Chewing gum	Oral	6 mg	Single doses, 30 minutes chewing	24
B	Nicorette® Freshfruit®	Chewing gum	Oral	4 mg	Single doses, 30 minutes chewing	
C	Nicorette® Freshfruit®	Chewing gum	Oral	2 mg	Single doses, 30 minutes chewing	
Duration of Treatment Visits in part I: 10 hours			**Time without NRT between visits in part I: ≥ 36 hours**			

Treatments in Part II of the Study

Treatment	Drug	Form	Route	Nicotine Dose	Regimen (every second hour)	#Subjects
D	Nicorette® Freshfruit®	Chewing gum	Oral	6 mg	Single dose, 2.5 minutes chewing	24
	Nicorette® Freshfruit®	Chewing gum	Oral	6 mg	Single dose, 20 minutes chewing	
	Nicorette® Freshfruit®	Chewing gum	Oral	6 mg	Single dose, 5 minutes chewing	
	Nicorette® Freshfruit®	Chewing gum	Oral	6 mg	Single dose, 10 minutes chewing	
E	Nicorette® Freshfruit®	Chewing gum	Oral	4 mg	Single dose, 2.5 minutes chewing	
	Nicorette® Freshfruit®	Chewing gum	Oral	4 mg	Single dose, 20 minutes chewing	
	Nicorette® Freshfruit®	Chewing gum	Oral	4 mg	Single dose, 5 minutes chewing	
	Nicorette® Freshfruit®	Chewing gum	Oral	4 mg	Single dose, 10 minutes chewing	
Duration of Treatment Visits in part II: 7 hours			**Time without NRT between visits in part II: ≥ 36 hours**			

Population(s) studied

24 Caucasian subjects, 15 male and 9 female aged 19-50 years, who smoked >15 cigarettes/day were included in the study.

23 subjects completed the study. There were three subjects with invalid PK parameters due to nicotine baseline concentrations ≥5 ng/mL at one, two or three of the treatment sessions. Data from the treatment occasions with valid PK parameter values from these three subjects were included in the PK and PD analyses. There were four subjects with incomplete data sets. All 24 included subjects were analysed for safety.

The amount of nicotine released from the used chewing gums was calculated by subtracting nicotine amounts in used gums from the average amount in unused gums (mean of 10 gums; obtained from the certificates of analysis).

Statistical methods

To compare Nicorette® Freshfruit® 6 mg gum with Nicorette® Freshfruit® 2 mg and 4 mg gum, respectively, 95% confidence intervals were calculated, using the mean square error (MSE) from the analysis of variance (ANOVA), for the ratio of the mean response of the primary response variables. The mixed linear model included period, sequence and treatment as fixed effects and subject within sequence as a random effect.

To further evaluate the linearity of the dose-response curves for nicotine cC_{max}, $cAUC_t$, and $cAUC_\infty$, the mixed linear models were refitted using the natural logarithm of dose as a (continuously varying) linear predictor of the log transformed PK parameters (as opposed to treating dose as a categorical variable with three levels). The regression coefficient, β say, for log dose was estimated and a corresponding 95% confidence interval was calculated. Thus, the hypothesis of a linear dose-response relationship corresponded to $\beta = 1$.

Descriptive summary statistics were presented for nicotine plasma concentrations, all PK parameters and the amount of nicotine released from the gums during 2.5, 5, 10, and 20 minutes (Part II) and 30 minutes (Part I). Summary measures were given for each treatment

and, where applicable, each measurement time. For continuous variables they included mean values, standard deviations, medians and maximum as well as minimum values. For t_{max} the frequency distribution was tabulated for each treatment.

Results

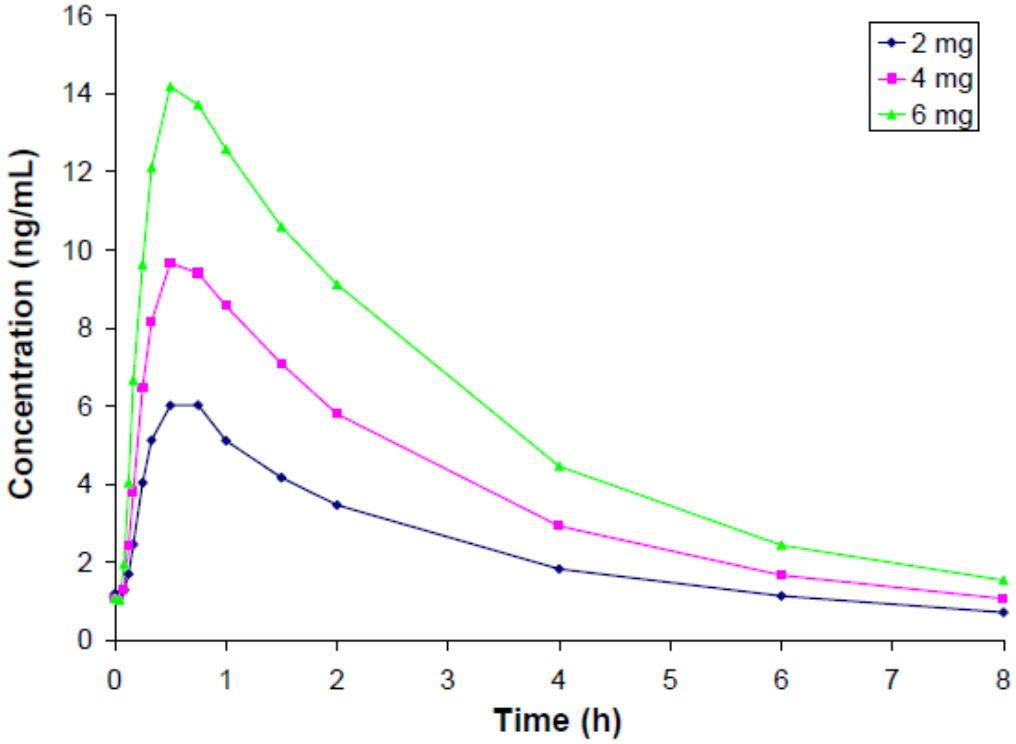


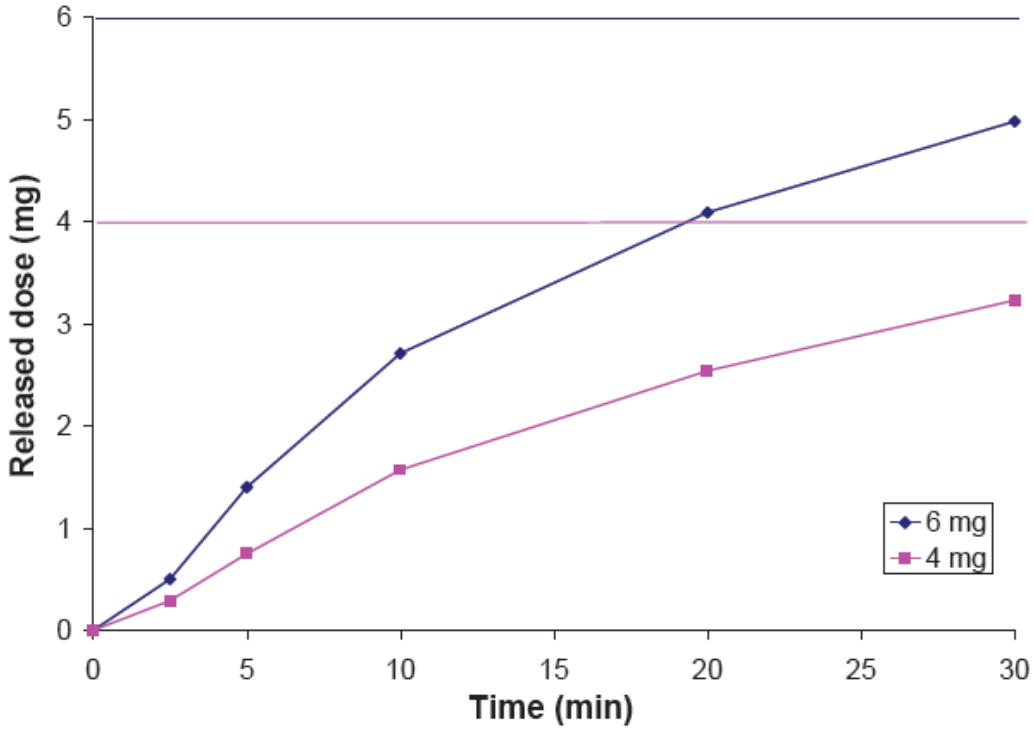
Figure 1: Mean Plasma Concentration versus Time Profiles.

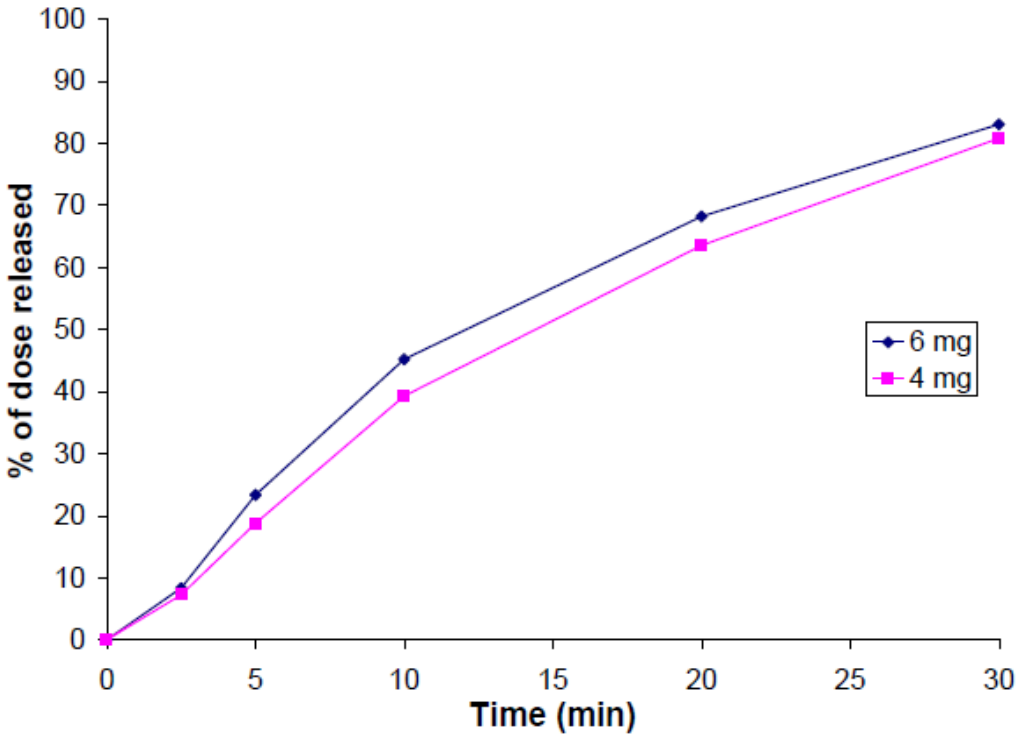
	cC_{max}	$cAUC_t$	$cAUC_\infty$
2 mg vs. 6 mg	38% (34-44)	35% (31-39)	36% (32-40)
4 mg vs. 6 mg	67% (59-76)	63% (56-71)	64% (57-72)

The statistical model investigating dose-linearity by estimating the regression coefficient for log cC_{max}/$cAUC_t$/cAUC vs. log dose showed that the regression coefficient was significantly different from 1 for cC_{max} but not for $cAUC_t$ and cAUC.

Amount of Nicotine Released from Gums

The figures below display the average released dose versus time profiles and the average fractional release versus time profile for the 4 mg and 6 mg Nicorette® Freshfruit® gums during 30 minutes of chewing.



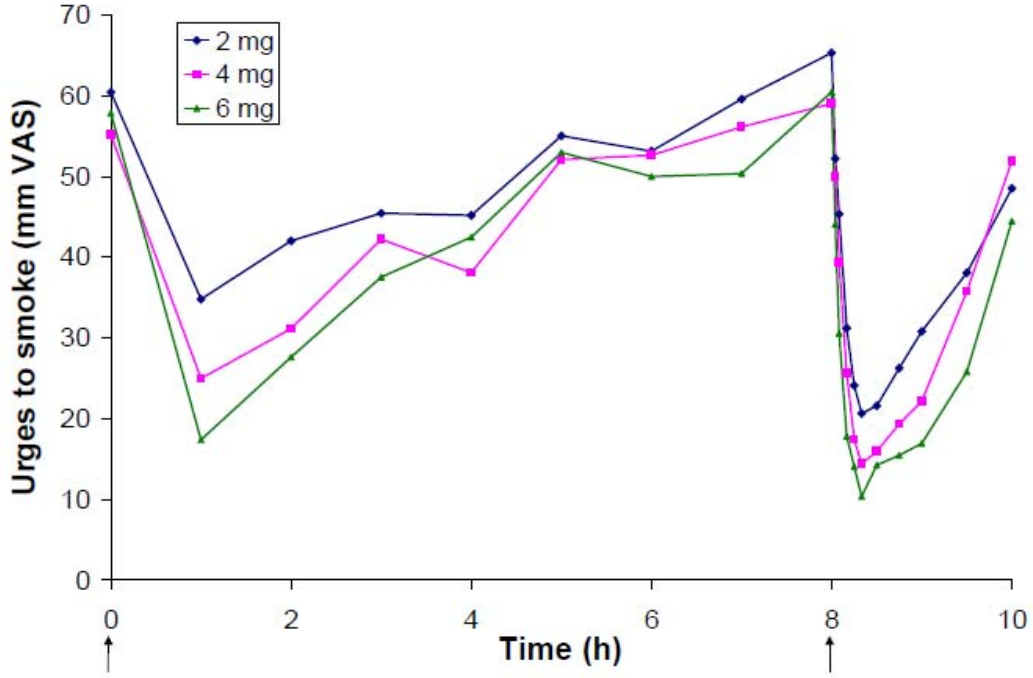


Mouth Irritation

Mouth irritation scores were as follows:

Dose	0 min	5 min	15 min	30 min	60 min
2 mg	0.0 ± 0.0	13.5 ± 20.4	19.5 ± 20.9	10.9 ± 17.7	0.9 ± 4.3
4 mg	0.6 ± 2.7	16.4 ± 19.6	23.8 ± 21.9	10.4 ± 10.9	2.0 ± 4.9
6 mg	1.2 ± 5.5	27.9 ± 20.9	28.0 ± 21.4	10.5 ± 11.3	1.5 ± 4.9

Urge to Smoke



There were no deaths, serious adverse events (SAEs) or other significant adverse events (AEs) in this study. A total of 124 treatment-emergent AEs were reported by 21 subjects. Ninety-nine (99) of these AEs were judged to be treatment-related. Fourteen of the treatment-related AEs were severe, 28 were moderate and 57 were of mild intensity.

Of the subjects with treatment related AEs, 4 were recorded for Nicorette Freshfruit® gum 2 mg, 11 for Nicorette Freshfruit® gum 4 mg and 17 for Nicorette Freshfruit® gum 6 mg. The body system most affected by AEs was the gastrointestinal tract with dyspepsia and salivary hypersecretion as the most frequently reported AEs. Hiccups were also common.

Conclusions

The PK parameters have been adequately calculated, summarised and analysed. The gums are seen to be essentially dose-proportional with regard to PK parameters and released dose.

It is noted that there was no significant difference between dose strengths with regard to craving reduction, although it is acknowledged that this study might not have been powered for such a comparison.

From an initial view of product safety profile, again there appears to be an essentially dose-related profile with regard to adverse events including mouth irritation. These events

were largely gastrointestinal in nature and known to be related to NRT products. Mouth irritation settled with exhaustion of the gum.

Study NICTDP1080

This was a single-dose comparative bioavailability study of crossover design comparing the PK profile of four oral NRT products in healthy volunteers.

Study design

Subjects were randomly allocated in equal proportions to one of four treatment sequences. Single doses of Nicorette Freshfruit® 6 mg gum, Nicorette Freshfruit gum 4 mg and 2 mg and NiQuitin Mint lozenge 4 mg were administered in a standardised mode, on four separate treatment visits. Periods without NRT, each lasting for at least 36 hours, separated the treatment visits.

The subjects abstained from smoking from 8 pm the evening before each visit and until the end of each visit. Blood for PK analyses was drawn before and at 2, 4, 6, 8, 10, 15, 20, 30, 45, and 60 minutes as well as at 1.5, 2, 4, 6, 8, 10, and 12 hours after drug administration. Subjects were monitored to capture any adverse events that occurred.

For treatment with a chewing gum, subjects were instructed to place the gum on the tongue and chew it once every 2 seconds for 30 minutes; a metronome was used to control the chewing rate. Subjects were also instructed to swallow saliva once every minute. Talking was not allowed during the chewing period.

For treatment with a lozenge, subjects were instructed to place the lozenge in their mouth, to occasionally move it from side to side until complete dissolution, and to not chew or swallow the lozenge. Talking was not allowed during dissolution time.

Test and reference products

Investigational Product	Vendor Lot ID / Batch Number	Formula Number
NMG 6 mg	MF997	N/A
Nicorette Freshfruit gum 4 mg	MF959A	N/A
Nicorette Freshfruit gum 2 mg	MH843A	N/A
NiQuitin Mint lozenge 4 mg	2022154	N/A

Population(s) studied

44 subjects, 25 male and 19 female aged 19-49 years, who smoked >15 cigarettes/day were included in the study.

41 subjects completed the study. After randomisation, two subjects withdrew due to adverse events and one subject for personal reasons. There were four subjects with invalid pharmacokinetic parameters due to nicotine baseline concentrations >5.0 ng/mL at one or more of the treatment sessions (data from 6 treatments were excluded). Data from the treatment sessions with valid PK parameter values from these subjects were included in the PK and PD analyses. Data from two additional treatments were excluded from PK and PD analyses since two subjects discontinued the treatment 25 minutes and 2 hours, respectively, following treatment start. Plasma concentration profiles from these treatments were too short to allow PK and PD evaluation.

Data from all included subjects were analysed with respect to safety information.

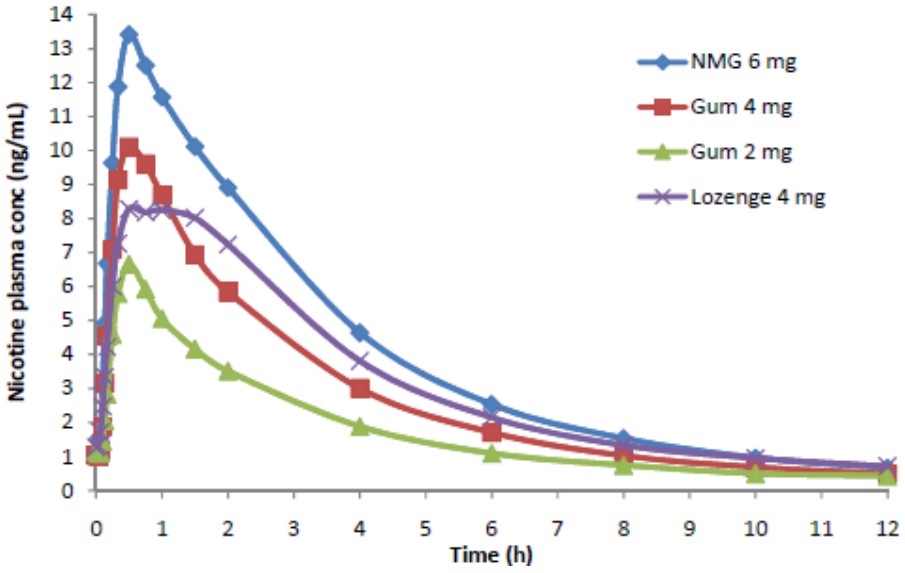
Statistical methods

Descriptive statistics (mean, standard deviation, median, minimum and maximum values) of the PK parameters were tabulated. For t_{max} the frequency distribution was tabulated for each treatment.

Pair-wise comparisons of Nicorette Freshfruit® 6 mg gum with Nicorette Freshfruit gum 2 mg, Nicorette Freshfruit gum 4 mg and with NiQuitin Mint lozenge 4 mg with respect to AUC_{10min}, cC_{max}, $cAUC_t$ and $cAUC_\infty$ were based on a mixed linear model for log transformed (natural log) PK data. The statistical model included sequence, treatment, and period as fixed effects, and subject, nested within sequence, as random effect. Additionally, for AUC_{10min} baseline plasma nicotine concentration (log scale) was included as a fixed effect. Confidence intervals for parameter mean ratios were derived using estimated means and residual variance estimates from the fitted model.

To further evaluate the linearity of the dose-response curves for Nicorette Freshfruit gum 2 and 4 mg, and Nicorette Freshfruit® 6 mg gum in terms of cC_{max}, $cAUC_t$ and $cAUC_\infty$, the mixed linear models were refitted using the natural logarithm of dose as a (continuously varying) linear predictor of the log transformed PK parameters (as opposed to treating dose as a categorical variable with three levels). The regression coefficient for log dose was estimated and a corresponding 95% confidence interval was calculated.

Results



	NMG 6 mg vs. Gum 4 mg	NMG 6 mg vs. Gum 2 mg	NMG 6 mg vs. Lozenge 4 mg
cC_{max}	134% (121-150)	233% (209-260)	144% (128-162)
$cAUC_t$	150% (134-167)	284% (255-315)	133% (119-149)
$cAUC_\infty$	147% (133-162)	266% (241-294)	130% (116-144)
AUC_{10min}	144% (124-167)	202% (174-234)	132% (113-153)

The statistical model estimating the regression coefficient for log $cC_{max}/cAUC_t/cAUC_\infty$ vs. log dose showed that the regression coefficient was significantly different from 1 for cC_{max} and $cAUC_\infty$, but not for $cAUC_t$.

Amount of nicotine Released from Gums

	NMG 6 mg	Gum 4 mg	Gum 2 mg
Mean±SD (Min-Max)	4.94 ± 0.69 (2.2-5.7)	3.36 ± 0.44 (1.7-4.0)	1.44 ± 0.39 (0.4-2.0)

Safety

There were no deaths, serious adverse events or other significant adverse events in this study.

A total of 53 treatment-emergent adverse events were reported. Thirty-three (33) of these adverse events were judged to be possibly, probably or very likely related to treatment. Four (4) of the treatment-related adverse events were categorized as severe, 16 were moderate and 13 were of mild intensity.

Of the subjects with treatment related adverse events, 10 were recorded for Nicorette Freshfruit® 6 mg gum, 7 for Nicorette Freshfruit gum 4 mg, 4 for Nicorette Freshfruit gum 2 mg, and 2 for NiQuitin lozenge 4 mg. The body system most affected by adverse events for the study treatments was the gastrointestinal tract with nausea being the most frequently reported adverse event.

Conclusions

Again, the gums are seen to be essentially dose proportional with regard to pharmacokinetic parameters and released dose. A similar profile is seen with regard to adverse events.

More nicotine appears to be released and absorbed from the equivalent gum formulation than the lozenge.

Study NICTDP1081

This was a multiple-dose comparative bioavailability study of crossover design comparing the steady state PK profile of three oral NRT products in healthy volunteers.

Study design

Multiple doses of Nicorette Freshfruit® 6 mg gum given either every 60 minutes (treatment A) or every 90 minutes (treatment C), respectively, Nicorette Freshfruit gum 4 mg given either every 60 minutes (treatment B) or every 90 minutes (treatment D), respectively, and NiQuitin Mint lozenge 4 mg given every 60 minutes (treatment E) were administered in accordance with labelling over 12 hours, on five separate treatment visits. Periods without NRT, each lasting for at least 36 hours, separated the treatment visits. The subjects abstained from smoking from 8 pm in the evening before each visit and until the end of each visit.

During treatments A, B and E, blood for PK analyses was drawn within 5 minutes before the first gum or lozenge was given (marking time zero) and immediately before the start of administrations at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11 hours. Thereafter samples were drawn at 5, 10, 15, 20, 30, 40, 50, and 60 minutes after the start of the last drug administration. During treatments C and D, blood was drawn within 5 minutes before the first gum was given and immediately before the start of administrations at 1.5, 3, 4.5, 6, 7.5, 9, and 10.5 hours. Thereafter samples were drawn at 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, and 90 minutes after the start of the last administration. Subjects were monitored to capture any adverse events that occurred.

For treatment with Nicorette Freshfruit® 6 mg gum and Nicorette Freshfruit 4 mg, subjects were instructed to place the gum in their mouth and chew it slowly with breaks as they considered most convenient for 30 minutes. Talking was not allowed during the chewing period.

For treatment with NiQuitin Mint lozenge 4 mg, subjects were instructed to place the lozenge in their mouth, to occasionally move it from side to side until complete dissolution, and to not chew or swallow the lozenge. Talking was not allowed during the dissolution time.

Population(s) studied

50 subjects, 25 male and 25 female aged 19-50 years, who smoked >15 cigarettes/day were included in the study.

After randomisation five subjects withdrew due to adverse events, two subjects withdrew for personal reasons, one subject was lost-to-follow-up and three withdrew for other reasons. There were 11 subjects with invalid PK parameters due to nicotine baseline concentrations >5.0 ng/mL at one or more of the treatment sessions (data from 23 treatments were excluded). Data from seven additional treatments were excluded due to other protocol deviations and data from eight treatments were excluded from PK and PD analyses because the treatment was terminated before the last dosing interval such that no PK parameters could be calculated.

Data from all included subjects were analysed with respect to safety information.

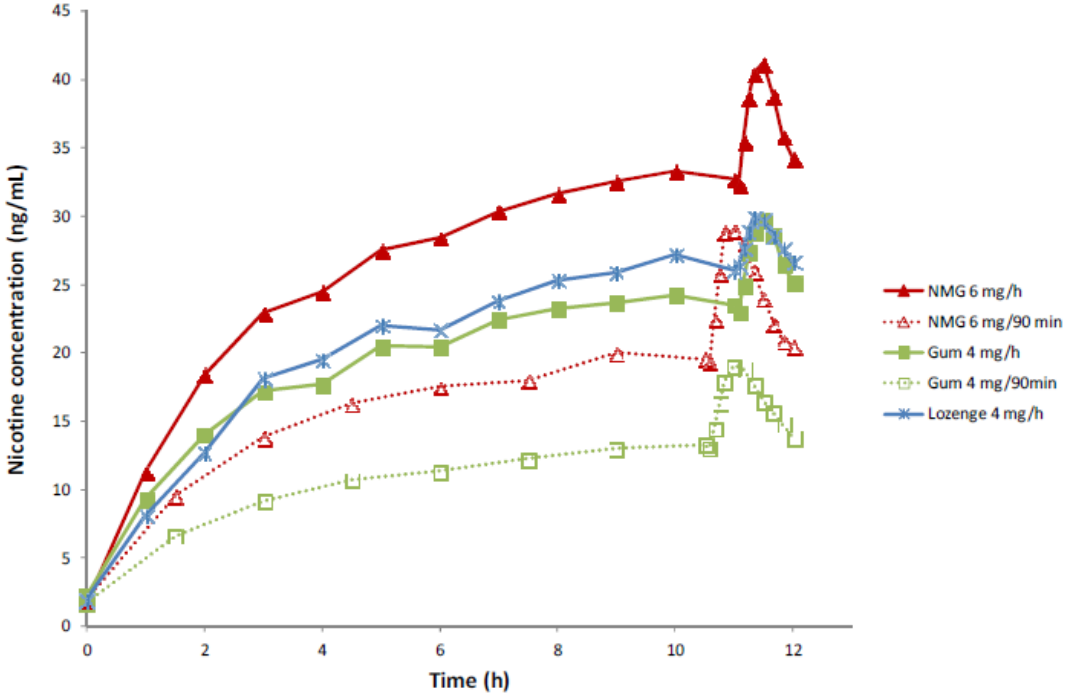
Statistical methods

Descriptive statistics (mean, standard deviation, median, minimum and maximum values) of the pharmacokinetic parameters were tabulated. For t_{max} the frequency distribution was tabulated for each treatment.

The statistical analyses of the PK parameters were separated into six pair-wise comparisons as described in the primary and secondary objectives. Each of the six pair-wise comparisons of the treatments with respect to C_{max}, C_{av} and AUC_{∞} was based on a linear model for log transformed (natural log) PK data. The statistical model included sequence, treatment, period and subject, nested within sequence as fixed effects. Confidence intervals for parameter mean ratios were derived using estimated means and residual variance estimates from the fitted model.

Given that subjects chewed the gum at their own convenience, the possible relationship between released amount of nicotine from the 6 mg gum and the amount of nicotine absorbed was investigated.

Results



	NMG 6 mg/h			NMG 6 mg/90 min		
	vs. gum 4 mg/h	**vs. lozenge 4 mg/h**	**vs. NMG 6 mg/90min**	**vs. gum 4 mg/90min**	**vs. gum 4 mg/h**	**vs. lozenge 4 mg/h**
C_{max} (ng/mL)	144% (129-161)	142% (127-158)	138% (123-154)	161% (145-180)	105% (94-117)	103% (92-115)
C_{av} (ng/mL)	143% (128-160)	136% (122-152)	150% (134-167)	158% (142-177)	96% (85-107)	91% (81-102)
AUC_{τ} (ng/mLxh)	as for C_{av}	as for C_{av}	100% (89-112)	as for C_{av}	143% (128-161)	136% (122-152)

The statistical model estimating the regression coefficient for log cC_{max}/$cAUC_t$/$cAUC_{\infty}$ vs. log dose showed that the regression coefficient was significantly different from 1 for cC_{max} and $cAUC_{\infty}$ but not for $cAUC_t$.

Amount of Nicotine Released from Gums

	NMG 6 mg/h	NMG 6 mg/90min	Gum 4 mg/h	Gum 4 mg/90min
Mean±SD (Min-Max)	4.4±1.3 (1.6-6.0)	4.6±1.1 (1.1-6.0)	3.0±0.7 (1.1-4.0)	2.8±0.8 (0.8-4.1)

Safety

There was one serious adverse event in this study which was categorised as depression. This serious adverse event, which appeared to be a worsening of a pre-existing depression that the subject had concealed at the screening investigation, was classified as possibly related to treatment (Nicorette Freshfruit® 6 mg gum /90 min and/or Gum 4 mg/h).

A total of 196 treatment-emergent adverse events were reported. One hundred and sixty-five (165) of these adverse events were judged to be possibly, probably or very likely related to treatment. Two (2) of the treatment-related adverse events were categorised as severe, 50 were moderate and 113 were of mild intensity.

Of the subjects with treatment-related adverse events, 39 were recorded for 6 mg/h gum, 22 for Nicorette Freshfruit gum 4 mg/h, 32 were recorded for 6 mg/90 min gum, 28 for Nicorette Freshfruit gum 4 mg/90 min and 44 for NiQuitin lozenge 4 mg/h.

The body systems most affected by adverse events for the study treatments were the respiratory, thoracic and mediastinal tract with hiccups being the most frequently reported adverse event and the gastrointestinal tract with abdominal distension and nausea being the most frequently reported adverse event.

There were no incidents or patterns indicating that the adverse event profiles of the NMG 6 mg treatments might differ qualitatively from those of other nicotine replacement products for use in the mouth. It was observed that more adverse events occurred with the 6 mg doses than with the 4 mg doses of the gums.

Conclusions

The PK parameters have been adequately calculated, summarised and analysed. Again, the gums are seen to be essentially dose-proportional with regard to PK parameters and released dose. The mean amount of nicotine released from NMG 6 mg and 4 mg appears to be constant over time upon once hourly dosing. The amount of nicotine released from NMG 6 mg is about 50% greater than that released from the 4 mg gum. In this study the 4 mg lozenge and the 4 mg gum appeared to release and lead to the absorption of similar amounts of nicotine.

Again, there appears to be an essentially dose-related profile with regard to adverse events, although these events were largely gastrointestinal in nature and known to be related to NRT products. However, it will be the effect on cravings which will determine the benefit-risk for this new higher dose strength.

IV.3 Pharmacodynamics

Study no. (Country)	No of subjects included (completed)	Gender (Male/ Female)	Race (W/B/A/O)	Average age (years), mean±SD (range)	Smoking years, mean±SD (range)	Cigarettes per day, mean±SD (range)	BMI (kg/m^2), mean±SD (range)
NICTDP1070	24 (23)	15/9	24/0/0/0	29.7 ± 9.5 (19 – 50)	12.5 ± 9.3 (2 – 36)	18.5 ± 2.1 (15 – 22)	22.7 ± 3.0 (19 – 30)
NICTDP2012	240 (228)	120/120	235/3/1/1	34.6±12.1 (19–55)	18.4±11.7 (2–41)	25.2±3.4 (21–38)	24.4±3.2 (17.8–31.9)

Abbreviations: BMI, Body Mass Index. W/B/A/O, White/Black/Asian/Other.

Study NICTDP2012

The primary objective of this study was to compare single-dose treatments with NMG 6 mg and Nicorette Freshfruit gum 4 mg with respect to urges to smoke during the first 1 and 3 hours, respectively, after onset of chewing, in healthy volunteer smokers.

Treatments comprised single doses of NMG 6 mg and Nicorette Freshfruit gum 4 mg, which were chewed during 30 minutes. All subjects were given both treatments on separate treatment visits in a crossover setting. Periods without NRT, each lasting for at least 36 hours, separated the treatment visits.

The subjects abstained from smoking from 8 pm in the evening before each visit and until the end of each visit. A carbon monoxide (CO) monitor was used as a rough indicator of abstinence from smoking during that time span. Subjects came to the investigation site at approximately 7.45 am on the study days. Breakfast was served at 8.30 am, and study treatments were given at about 9.30 am. The subjects chewed the gums according to instructions from the study personnel. After chewing, used gums were collected for nicotine analysis. Electronic diaries were used to record the time of start of administration, and to collect urges to smoke and product acceptability data. Urges to smoke were scored on a 100 mm VAS before the start of treatment and during 5 hours thereafter. Subjects were also monitored to capture any adverse events. At the end of each visit, subjects filled in a questionnaire on product acceptability.

For treatment with NMG 6 mg and Nicorette Freshfruit 4 mg, subjects were instructed to place the gum in their mouth and chew it slowly with breaks as they considered most convenient for 30 minutes.

Population Studied

Two-hundred and forty (240) subjects, 120 males and 120 females, were included in the study. Two-hundred and thirty-five subjects were White, three were Black, one was Asian and one was of other origin. The subjects were smokers consuming an average of 25 cigarettes per day (range 21-38 cigarettes) and had been smokers for 18 years on average (range 2-41 years). Their average age was 35 years (range 19-55 years), and their average BMI was 24 kg/m^2 (range 18-32 kg/m^2).

All subjects were healthy adult volunteers. None of the subjects had conditions or a medical history that the investigator considered sufficient to affect the interpretability of study results or to represent a potential risk to the subject during study participation.

After randomisation, two subjects withdrew due to adverse events, nine subjects withdrew for personal reasons and one for other reasons.

Statistical Analysis Plan

Pair-wise treatment comparisons with respect to AUC_{1h} and AUC_{3h}, *i.e.* the area under the urges to smoke-*vs.*-time curve from time zero (baseline) until 1 hour and until 3 hours, were based on a mixed linear model including sequence, treatment, site and period as fixed effects, and subject, nested within sequence, as random effect. Additionally, the baseline urges to smoke score at time zero were included as a co-varying fixed effect. The baseline urges to smoke score was calculated as the average of the three pre-treatment assessments.

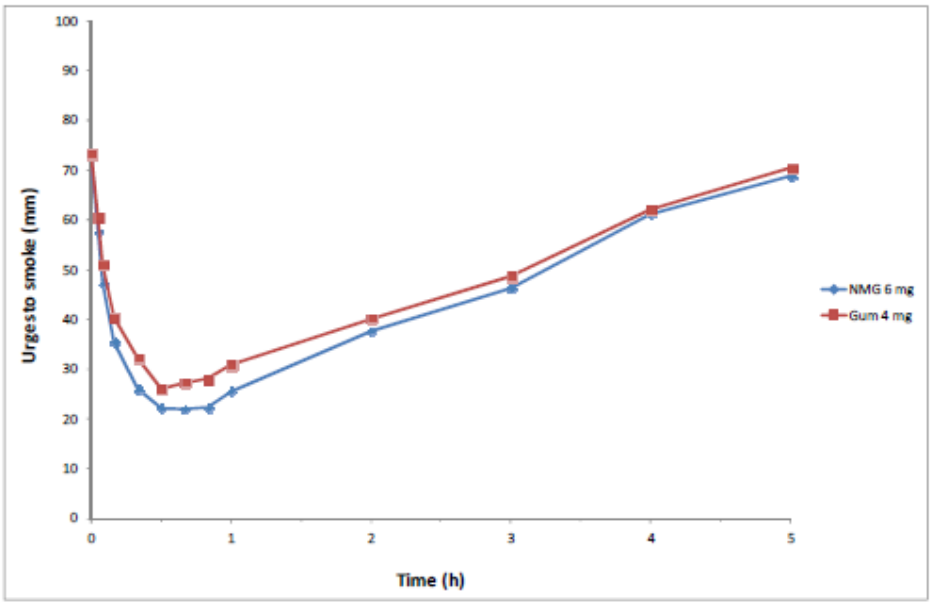
For the pair-wise treatment comparisons with respect to AUC_{3min}, AUC_{5min}, AUC10min, AUC_{2h}, AUC4h, AUC_{5h}, were based on a mixed linear model including sequence, treatment, site and period as fixed effects, and subject, nested within sequence, as random effect. Additionally, the baseline urges to smoke score at time zero was included as a co-varying fixed effect.

Pair-wise treatment comparisons of ordered categorical-scale assessments of acceptability were evaluated with the Wilcoxon signed-rank test applied to derived treatment differences.

Results

Time	Mean average score change from baseline (mm)		
	NMG 6 mg	Gum 4 mg	NMG 6 mg vs. Gum 4 mg
3 min	-7.2±9.0	-6.1±8.7	-1.1 [-2.2, -0.1], p 0.034
5 min	-12.2±13.4	-10.4±12.9	-1.9 [-3.4, -0.4], p 0.016
10 min	-21.8±18.6	-18.7±17.5	-3.1 [-5.0, -1.2], p 0.001
60 min	-43.9±23.8	-39.3±23.3	-4.8 [-7.0, -2.6], p<0.001*
120 min	-42.7±23.6	-38.7±23.7	-4.2 [-6.2, -2.1], p<0.001
180 min	-38.8±23.2	-35.5±23.4	-3.4 [-5.8, -1.0], p 0.004*
240 min	-33.9±22.6	-31.1±22.7	-2.9 [-5.0, -0.7], p 0.008
300 min	-28.7±21.8	-26.3±21.5	-2.5 [-4.6, -0.4], p 0.021

Mean Urge to Smoke vs Time (VAS)



Amount of Nicotine Released from Gums (mg)

	NMG 6 mg	Gum 4 mg
Mean ± SD	4.00 ± 1.28	2.64 ± 0.90
(Min - Max)	(0.3-6.2)	(-0.1-4.2)

Safety

There were no serious adverse events in this study. A total of 173 treatment-emergent adverse events were reported. One hundred and fifty-two (152) of these adverse events were judged to be possibly, probably or very likely related to treatment. None of the treatment-related adverse events were categorised as severe, 17 were moderate and 135 were of mild intensity.

Ninety-five (95) subjects recorded treatment-related adverse events with NMG 6 mg, and 57 with Nicorette Freshfruit gum 4 mg.

The body systems most affected by adverse events associated with the study treatments were the gastrointestinal tract, with nausea and dyspepsia being the most frequently reported adverse event and the respiratory tract, and thorax and mediastinum, with throat irritation and hiccups being the most frequently reported adverse event.

Conclusions

NMG 6 mg reduced the urges to smoke by a mean 44 mm on the VAS over the first 60 minutes and 39 mm over the first 3 hours after administration. These reductions were statistically significantly greater than with Nicorette Freshfruit gum 4 mg, with a mean reduction of 40mm and 36mm respectively ($p< 0.001$; $p= 0.004$). Based on a single dose, a similar proportion of the nicotine content of the gums was released.

In heavy smokers it is likely that either a cigarette will be smoked or a form of NRT used approximately every hour. Therefore, it is the clinical significance of an effect size on the VAS up to 1 hour which is of relevance to the intended population. It is acknowledged that the nicotine from NMG 6mg is more rapidly released and absorbed than that from the 4mg gum and this translates to a more rapid onset of craving relief. By ten minutes, this has achieved a between treatment mean difference of 3.1mm on the VAS and 4.8mm by 1 hour.

There is a clear dose dependent relationship regarding the adverse event profile of the gum formulations. While these adverse events are qualitatively similar to those documented for other oral forms of NRT, they are present with increased frequency. This has to be considered in the context of there being little, if any, clinically significant benefit.

The applicant is asked therefore to further discuss the clinical relevance of the effect size.

IV.4 Clinical efficacy

The clinical efficacy data that were part of Study NICTD1070 and Study NICTDP2012 are discussed in the above sections.

IV.5 Clinical safety

The safety of the test product NMG 6 mg has been evaluated in the three Phase I pharmacokinetic studies and one Phase II pharmacodynamic study, described above. A total of 342 healthy smokers received at least one dose of test product NMG 6 mg during the clinical development program:

Study no.	No of subjects exposed to NMG 6 mg§ (Total included)	Treatment duration*	Dose (range)
NICTDP1070	24 (24)	5 visit days Part I: 10 h/day Part II: 7 h/day (≥36 h wash out)	64 mg / 5 visits (2 mg – 24 mg/ visit)
NICTDP1080	42 (44)	4 visit days 12 h/day (≥36 h wash out)	16 mg/ 4 visits (2 mg – 6 mg/ visit)
NICTDP1081	44 (50)	5 visit days 12 h/day (≥36 h wash out)	248 mg / 5 visits (48 mg – 72 mg/ visit)
NICTDP2012	232 (240)	2 visit days 5 h/visit (≥36 h wash out)	10 mg/ 2 visits (4 - 6 mg/visit)

§ Subjects who received at least one dose of NMG 6 mg.
* All studies had wash-out periods of at least 36 hours.

The safety of nicotine from NRT is well-characterised in the literature. In general, NRT products are associated with a number of adverse events, including - but not limited to - headache, mouth/throat irritation, dyspepsia, cough, rhinitis, flatulence, gum problems, diarrhoea, hiccups, nausea, taste disturbance, tooth disorder, jaw/neck pain and sinusitis. Allergic reactions are known to occur in people who use NRT, but considering all formats and severities collectively (including symptoms of anaphylaxis), such events occur rarely (less than 1 in 10,000).

The safety data collected across the PK/PD studies for the test product 6 mg gum showed that, although more adverse events were reported following use of the 6 mg gum, there was no significant difference in the adverse event profile compared to that for Nicorette Freshfruit Gum 2 mg or 4 mg. Adverse events that affect the gastrointestinal and respiratory systems

were the most frequently reported adverse events. Similar results were observed for the reference NRT products used in the studies; i.e. Nicorette Freshfruit Gum 2 mg and 4 mg and Nicotine Mint Lozenge 4 mg. Hiccups and abdominal distention were the most commonly reported treatment-related adverse events, followed by nausea, throat irritation and dizziness. All of the treatment related adverse events were mild or moderate in severity and resolved on discontinuation of treatment.

IV.6 Risk Management Plan (RMP)

The marketing authorisation holder has submitted an RMP in accordance with the requirements of Directive 2001/83/EC, as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to these products.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below.

Safety Concern	Routine risk minimisation activities sufficient?	Description/Justification
Important identified risks	N/A	
Important potential risks	N/A	
Important missing information: Relatively limited safety information in sub-population of patients with: a) Recent myocardial infarction b) unstable angina (including Prinzmetal´s angina) c) Cardiac arrhythmias d) uncontrolled hypertension e) recent stroke	Yes	Routine risk minimisation activities with increased frequency of monitoring using SMQs and MedDRA groupings for screening and further review of reported cardiovascular AEs in these subpopulations (see also Section 2.3)

IV.7 Discussion on the clinical aspects

The safety profile of nicotine replacement therapy (NRT) is well-characterised. It is noted that the reported adverse events are qualitatively similar to those documented for other oral forms of NRT, although they are present with a seemingly dose-dependent increased frequency. It is acknowledged that smokers self-titrate their intake of nicotine as required, and that the potential risks of the use of NRT are far less than the risks associated with smoking. The grant of a marketing authorisation is recommended for this application from a clinical perspective.

V USER CONSULATATION

A user consultation with target patient groups on the PIL has been performed and the results submitted in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the patient information leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are

able to act upon the information that it contains.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk assessment is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for products granted marketing authorisations are available on the MHRA website.

The currently approved labels are presented below:


nicorette
fruitfusion 6mg gum
nicotine
for smokers of more than 20 cigarettes a day
100 pieces sugar-free coated gum
coated gum
sugar-free
fruitfusion
nicorette
fruitfusion
6mg gum
nicotine
6mg
for smokers of more than 20 cigarettes a day
for relief of cravings and nicotine withdrawal symptoms
for smokers of more than 20 cigarettes a day
100 pieces
4 packs of 25
Batch No:
Use before:
nicorette
fruitfusion 6mg gum
nicotine
for smokers of more than 20 cigarettes a day
100 pieces sugar-free coated gum
nicorette fruitfusion 100 pieces
NICORETTE® fruitfusion 6mg gum relieves and/or prevents withdrawal symptoms including strong cravings experienced when trying to stop smoking or cutting down on cigarettes. It provides a safer alternative to smoking for both the individual and those around them. Ideally you should aim to stop smoking. However, this product can be used either to completely replace all your cigarettes, or if you do not feel ready to stop smoking completely, to replace certain cigarettes and therefore help you to cut down. It may also help increase your motivation to quit.
Directions: Children aged between 12 to 18 years, should consult with a doctor, nurse or pharmacist before starting to use this product.
Please read the enclosed leaflet carefully before starting to use the product and note the chewing technique. Chew one piece of gum when you feel the urge to smoke.
Do not use more than 15 pieces a day.
Warning: Do not exceed the stated dose.
If you are pregnant, or you need any other advice before using this product, talk to your doctor, pharmacist or nurse.
NICORETTE® chewing technique:
1. Chew slowly until taste becomes strong.
2. Rest between gum and cheek.
3. Chew again when taste has faded.
Do not use if you are allergic to any of the ingredients listed below.
You are more likely to quit smoking when using this product with help from your pharmacist, doctor, a trained counsellor or a support programme.
Contents: This pack contains 100 pieces of fruit flavour chewing gum, each containing 6mg nicotine. Also includes: Chewing gum base, E967, peppermint oil, E500, E950, menthol, E530, Tutti-frutti flavour, E464, E955, E433, acacia, E171, E903, E321.
Storage: Keep out of reach and sight of children. Store in original container to protect from light. Dispose of sensibly.
McNeil
PL Holder: McNeil Products Ltd,
Maidenhead, Berkshire, SL6 3UG, UK.
PL 15513/0381


McNeil AB
BRAND: Nicorette Gum SPINNAKER 4
DATE: 2012-12-04/NBE-e
ARTICLE No: 823076
DESCRIPTION: Freshfruit 6mg 200st
REPLACES No: -
COUNTRY: England/GB
SIZE: 105 x 101 x 90 mm
PMS COLORS: 348 362 Black 1235 1575
LAF = LABELING APPROVAL FORM
REGISTRATION DEPARTMENT
MARKETING DEPARTMENT
nicorette
fruitfusion 6mg gum
nicotine
for smokers of more than 20 cigarettes a day
200 pieces sugar-free coated gum
coated gum
sugar-free
fruitfusion
6mg
for relief of cravings and nicotine withdrawal symptoms
for smokers of more than 20 cigarettes a day
200 pieces
8 packs of 25
Batch No:
Use before:
nicorette fruitfusion 200 pieces
Warning: Do not exceed the stated dose.
Storage: Keep out of reach and sight of children. Store in original container to protect from light. Dispose of sensibly.
PL Holder: McNeil Products Ltd, Maidenhead, Berkshire, SL6 3QG, UK
PL 15513/0381


823217
nicorette
fruitfusion 6mg gum
nicotine
for smokers of more than 20 cigarettes a day
105 pieces sugar-free coated gum
coated gum
sugar-free
fruitfusion
nicorette
fruitfusion
6mg gum
nicotine
6mg
for relief of cravings and nicotine withdrawal symptoms
105 pieces
for smokers of more than 20 cigarettes a day
3 574661 090405
PL 15513/0381
PL Holder: McNeil Products Ltd.
Maidenhead, Berkshire, SL6 3UG, UK.
Use by:
Batch No:
McNeil
BRAND: Nicorette Gum SPINNAI
DATE: 2013-08-06/MPS-d
ARTICLE No: 823217
DESCRIPTION: Freshfruit 6mg 105st
REPLACES No: --
COUNTRY: England/GB
SIZE: 66 x 57 x 112 mm
PMS COLORS: 348 362 Black 1235 1575
nicorette fruitfusion 105 pieces
NICORETTE® fruitfusion 6mg gum relieves and/or prevents withdrawal symptoms including strong cravings experienced when trying to stop smoking or cutting down on cigarettes. It provides a safer alternative to smoking for both the individual and those around them. Ideally you should aim to stop smoking. However, this product can be used either to completely replace all your cigarettes, or if you do not feel ready to stop smoking completely, to replace certain cigarettes and therefore help you to cut down. It may also help increase your motivation to quit.
Directions: Children aged between 12 to 18 years, should consult with a doctor, nurse or pharmacist before starting to use this product.
Please read the enclosed leaflet carefully before starting to use the product and note the chewing technique.
Chew one piece of gum when you feel the urge to smoke.
Do not use more than 15 pieces a day.
Warning: Do not exceed the stated dose.
If you are pregnant, or you need any other advice before using this product, talk to your doctor, pharmacist or nurse.
NICORETTE® chewing technique:
1. Chew slowly until taste becomes strong.
2. Rest between gum and cheek.
3. Chew again when taste has faded.
Do not use if you are allergic to any of the ingredients listed below.
You are more likely to quit smoking when using this product with help from your pharmacist, doctor, a trained counsellor or a support programme.
Contents: This pack contains 105 pieces of fruit flavour chewing gum, each containing 6mg nicotine. Also includes: Chewing gum base, E967, peppermint oil, E500, E950, menthol, E530, Tutifrutti flavour, E464, E965, E433, acacia, E171, E903 and E321.
Storage: Keep out of reach and sight of children. Store in original container to protect from light. Dispose of sensibly.


013-08-06/MPS-d
No: 823218
TION: Freshmint 4mg 210st
S No: --
Y: England/GB
x 108 x 75 mm
348
362
Black
1235
1575
nicorette
fruitfusion 6mg gum
nicotine
for smokers of more than 20 cigarettes a day
210 pieces sugar-free coated gum
3 574661 090412
coated gum
sugar-free
fruitfusion
nicorette
fruitfusion
6mg gum
nicotine
TM
6mg
for relief of cravings and nicotine withdrawal symptoms
for smokers of more than 20 cigarettes a day
210
pieces
823218
nicorette
fruitfusion 210 pieces
NICORETTE® fruitfusion 6mg gum relieves and/or prevents withdrawal symptoms including strong cravings experienced when trying to stop smoking or cutting down on cigarettes. It provides a safer alternative to smoking for both the individual and those around them. Ideally you should aim to stop smoking. However, this product can be used either to completely replace all your cigarettes, or if you do not feel ready to stop smoking completely, to replace certain cigarettes and therefore help you to cut down. It may also help increase your motivation to quit.
Directions: Children aged between 12 to 18 years, should consult with a doctor, nurse or pharmacist before starting to use this product.
Please read the enclosed leaflet carefully before starting to use the product and note the chewing technique. Chew one piece of gum when you feel the urge to smoke.
Do not use more than 15 pieces a day.
Warning: Do not exceed the stated dose.
If you are pregnant, or you need any other advice before using this product, talk to your doctor, pharmacist or nurse.
NICORETTE® chewing technique:
1. Chew slowly until taste becomes strong.
2. Rest between gum and cheek.
3. Chew again when taste has faded.
Do not use if you are allergic to any of the ingredients listed below.
You are more likely to quit smoking when using this product with help from your pharmacist, doctor, trained counsellor or a support programme.
Contents: This pack contains 210 pieces of fruit flavour chewing gum, each containing 8mg nicotine. Also includes: Chewing gum base, E967, peppermint oil, E500, E950, menthol, E330, Tutifrutti flavour, E484, E955, E433, acacia, E171, E903 and E321.
Storage: Keep out of reach and sight of children. Store in original container to protect from light. Dispose of sensibly.
McNeil
PL Holder: McNeil Products Ltd.
Maidenhead, Berkshire, SL6 3UG, UK.
PL 15513/0381
nicorette
fruitfusion 6mg gum
nicotine
for smokers of more than 20 cigarettes a day
210 pieces sugar-free coated gum
nicorette
fruitfusion
6mg gum
LAF - LABELING APP
REGISTRATION DEPARTMENT
We hereby confirm that
Text
Spelling
Codes
Name and Address (Licence holder)
Licence No.: (Market authorisation No.)
Country
Date / Sig
MARKETING DEPARTMENT
We hereby confirm that
Design
Date / Signature / Country:
By signing the attached artwork the market confirm that this
the correctness of all aspects (text, dosage values, spelling, f
the concerned parts must be marked clearly. The market appr
print the content for this proof. The market takes full responsi


nicorette
fruitfusion 6 mg
nicotine
medicated chewing gum
McNeil
950977

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report

(Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)

Annex 1

Public Assessment Report

Pharmacy to General Sales List Reclassification

Nicorette FruitFusion 6mg Gum

(Nicotine resinate)

PL 15513/0381

McNeil Products Limited

TABLE OF CONTENTS

APPLICATION FOR CLASSIFICATION OF NICORETTE FRUITFUSION 6mg GUM (Nicotine resinate) AS GSL

MA no.	PL 15513/0381
Product name	Nicorette Fruitfusion 6mg gum

INTRODUCTION

Background

This application seeks to obtain an MA and also classify the product as GSL for the relief of nicotine craving and withdrawal symptoms as an aid to smoking cessation in highly dependent adults and children aged 12 and over. The proposed use in children and adolescents should be discussed with a Healthcare Professional (doctor, nurse, pharmacist). In addition it would be indicated for "harm reduction"

- to aid smokers wishing to reduce prior to quitting
- to assist smokers unwilling or unable to smoke
- as a safer alternative to smoking for smokers and those around them.

It would also be indicated in pregnant and lactating women and, if possible, should be used in conjunction with behavioural support.

It should be noted that CHM, endorsed by the Licensing Authority, recommended the "harm reduction" indication for all NRT products that were on the market in 2009. However, it was stated that new formulations, such as Nicorette Fruitfusion 6mg gum, would need to be assessed for this indication on a case-by-case basis.

Currently all the different formulations of nicotine containing medicinal products available in the UK have GSL status but some were originally either POM or P. Nevertheless, different strengths (such as Nicorette 25mg Invisi patch) and formats (such as the Nicorette Combi – [Nicorette Invisi patch (15mg) plus Nicorette icy white gum (2mg)], Nicorette nasal spray and Nicorette QuickMist Mouthspray) were granted GSL status at the time of authorization.

As this is a new higher strength formulation of nicotine containing gum the suitability for GSL status is being assessed.

Proposed dose schedule

The product would be for highly dependent smokers (in excess of 20 cigarettes/day). The SmPC recommends:

- if 20 cigarettes/day or fewer are smoked/day the 2mg gum is indicated
- if more than 20/day are smoked the 4mg or 6mg gum will be required
- but the 6mg gum "can be recommended particularly to those requiring enhanced craving relief compared to the 4mg gum".

The individual should use the product whenever they feel to urge to smoke or to prevent cravings in a situation where they are likely to occur with a maximum daily dose of 15 pieces. Smokers are also advised to aim to quit smoking completely as soon as possible.

Proposed "enhanced" post-marketing surveillance

As with other NRT products permitted GSL status at the time of MA grant, the applicant is proposing the following measures (relating mainly to potential abuse/misuse) if Nicorette Fruitfusion 6mg gum is authorised with GSL status:

- regular monthly meeting when the applicant will monitor for signals suggesting inappropriate use (abuse/misuse)
- annual PSURs for the first 3 years
- specific section in each PSUR relating to abuse/misuse
- routinely monitored sales data.

CLINICAL ASSESSMENT

Pharmacokinetic (PK) profile

Assessment indicates that:

- the PK parameters had been adequately calculated, summarised and analysed.
- The gums (2mg: 4mg: 6mg) are essentially dose proportional in respect of PK parameters and released dose.

Efficacy

The data showed that nicotine is more rapidly released and absorbed from the 6mg than from the 4mg gum, however, initially there were concerns relating to the clinical relevance of the effect on craving in the heavy smoking population. Additional data were requested which were reassuring in that as the difference in relief of urge to smoke between the 6mg and 4mg gum was of similar magnitude to that between the 4mg and 2mg strengths. It is not unreasonable to expect that a proportionally greater relief of the urge to smoke might also translate into a higher number of successful quit attempts.

Conclusion

It is not only quit attempts that are at issue. The indication is for harm reduction so regardless of quit attempts, replacement of cigarettes with medicinal nicotine would benefit both the individual smoker and, depending on the situation on where smoking occurs, those exposed to second- and third-hand smoke.

Safety

The safety profile of NRT is well characterized and the reports of AEs are "qualitatively similar to those documented for other forms of NRT". However, there was an apparent dose-dependent increase in frequency but there were no significant differences in the profile of AEs reported with the 2mg and 4mg gum, and these were typical of those known to be associated with NRT.

Conclusion

Smokers are adept at self-titrating nicotine levels as required, to meet their needs and any potential risk of NRT is far less than the risks of smoking.

CRITERION FOR GSL STATUS

A GSL medicine is one that "can with reasonable safety be sold or supplied otherwise than by or under the supervision of a pharmacist." (Human Medicine Regulation 2012, regulation 62(5)). "Reasonable safety" has been defined as "where the hazard to health, the risk of misuse and the need for special handling precautions are all small, and where wider sale would be a convenience to the purchaser".

MEDICAL ASSESSMENT OF SUITABILITY FOR GSL AVAILABILITY

Rationale for classification as GSL

The applicant outlines the potential dangers of smoking and the benefits of quitting but also points out the low success rates of a quit attempt. NRT may help the latter as from a meta-

analysis of 111 randomised controlled trials identified, the Cochrane collaboration **(Stead et al 2008)** concluded that the relative risk (RR) of abstinence at 6 months for any form of NRT was 1.58 (95% CI:1.50 to 1.66). Other studies demonstrate that high-dose NRT or a combination of NRT products increase quit success rates compared with those containing lower doses of nicotine. The applicant considers that those who need a high degree of nicotine substitution to suppress cravings would benefit from a NRT gum containing 6mg of nicotine, and for maximum potential benefit this extension to the range of NRTs should be as widely available as possible.

5.2 Characteristics (pharmacokinetic: clinical) of the 6mg gum

The MAH points out that:

- absorption of nicotine from Nicorette Fruitfusion 6mg gum is slower than that from smoking a cigarette
- the Cochrane review concluded from 53 placebo-controlled studies on NRT gum, that for smoking cessation the RR at 6 months or more is 1.43 (95% CI: 1.33-1.53). For the 4 trials directly comparing 4mg and 2mg nicotine containing gum in highly dependent smokers, the pooled estimate suggests a significant benefit from the higher dose – RR 1.85 (95%CI: 1.36-2.50).

5.3 Hazard to health

It is noted that although Nicorette Fruitfusion 6mg gum is not bioequivalent to any existing NRT, plasma levels are comparable to those obtained from the 2mg and 4mg formulations. The most reported AEs were nausea, dyspepsia, throat irritation and hiccups which occurred with an increased frequency than with the 4mg gum but from the studies none of the treatment-related AEs were considered severe and no serious AEs were reported. In addition most AEs (particularly mouth and throat irritation) occurred in the early days of use with users becoming tolerant to these with time.

5.4 Indirect risk

The applicant considers there to be no risk of masking and/or delaying diagnosis of any underlying disease or condition.

5.5 Dependence and abuse potential

As part of an update/harmonization of NRT product information a standard statement re transferred dependence ("**Transferred dependence is rare and is both less harmful and easier to break than smoking dependence**") was included in the SmPC of NRT products. Although the potential for dependence increases for products from which nicotine is rapidly absorbed with subsequent high peak levels, from the AE data in the most recent PSUR, the applicant considers that there is no indication that the dependence potential for Nicorette gum does not differ from other NRT products. In addition from a "comprehensive literature search", despite the paucity of published material, that which there is reflects the PSUR findings.

The fact that Nicorette Fruitfusion 6mg gum does not result in rapidly achieved high arterial plasma levels militates against a high degree of dependence and/or abuse as does the recommendation not to use more than 15 pieces per day. As additional re-assurance the MAH propose enhanced post-marketing surveillance (see section 1.3 above).

5.6 Overdose

The applicant states that if overdose should occur, early symptoms such as nausea and/or vomiting are likely to limit further use. In addition, most smokers self-regulate their plasma

nicotine levels within a fairly narrow range. In studies where smokers used NRT but continued to smoke they did not exceed "tolerable levels". In addition other data indicate that "the potential for overdose with NRT products is minimal and does not pose a significant health risk."

Conclusion
The information on overdose in NRT SmPCs has been updated to reflect that in Toxbase. Relevant information has now been included (eg potential dangers in a young child) and potentially dangerous information (*e.g.* use of activated charcoal without any restrictions). This is satisfactory.

It should be noted that revision of this section does not affect either the PIL or label.

Convenience to the consumer

The aim of the current formulation is to provide a nicotine gum that has a faster onset and a longer lasting effect than those currently available. This is likely to be of benefit to the highly dependent smoker and GSL availability would permit much easier access than would be available if the legal classification were to be P or POM.

Supervision of a Pharmacist

The applicant has not specifically discussed the role of the pharmacist in supervising the sale of the product and measures to manage safe use as a GSL product. Nicotine containing gums have been available without pharmacist supervision for many years and whilst this is a new higher strength product, the labelling provides clear information about who should use the product and how to use it. Under these circumstances, pharmacist supervision is not considered necessary.

Conclusion
The product brand 'Nicorette' is familiar and has long been associated with the range of NRT products already available GSL. Although the product has a higher strength, it is clearly labelled, and the labelling and the patient information leaflet include advice that the product is aimed at highly dependent smokers (in excess of 20 cigarettes a day).

Furthermore, both the indication and safety profile are unchanged from other GSL NRT products and as smokers are known to titrate the dose of these products to their needs the risk of new safety concerns without pharmacy supervision is considered to be low.

Overall GSL supply is considered appropriate and the product should be available on self-selection, and will benefit more dependent smokers in particular.

PRODUCT INFORMATION

SmPC

The SmPC is appropriate, includes the "harm reduction" indication, is in line with other similar products and, therefore, is acceptable.

Patient Information Leaflet

This is in line with SmPC and patient information for other NRTs and is acceptable.

Label

This is appropriate for a GSL product and is acceptable.

DISCUSSION

Nicorette Fruitfusion 6mg gum is not bioequivalent to an existing GSL NRT but the PK parameters and released dose essentially show dose proportionality to the two currently available lower strength gums (2mg:4mg). This has been translated into a difference (increase) in relief of urge to smoke between the 6mg and 4mg gum that was of similar magnitude to that between the 4mg and 2mg strengths. However there was, not unexpectedly, an apparent dose-dependent increase in frequency of AEs but these were typical of other NRTs, and from the studies none of the treatment-related AEs were considered severe and no serious AEs were reported. Most AEs occurred early with users becoming tolerant over time, and no new safety issues have been identified which would be affected by GSL availability of the product.

The levels of nicotine achieved by use of Nicorette Fruitfusion 6mg gum and the expected safety profile give no indication that this product would pose more of a hazard to health than other NRT products currently available on GSL. The product has no particular characteristics that make the risk of misuse more likely than other NRTs. In addition, the applicant proposes to implement appropriate monitoring. The product information contains clear directions on responsible handling and disposal in order to prevent accidental exposure and the revised overdose section provides appropriate advice to HCPs in the unlikely event of this occurring. The essential proportionality of PK and safety profile to other GSL NRT products is balanced by increased "efficacy" and considerably less nicotine availability than achieved from cigarettes, so the strong likelihood is that Nicorette Fruitfusion 6mg gum could be supplied and used with reasonable safety without the supervision of a pharmacist.

CONSULTATION

Previous policy had been to consult on new higher strengths of proposed GSL products. Following publication of the revised Reclassification Guideline in 2012 however, where the reclassification is not major (such as first in class or first time P/GSL indication, decisions to consult are taken on a case-by-case basis.

Whilst reclassification of this product reflects an extension to an existing GSL availability, there is no reason to consider it is a major change. Importantly, the medical assessment has not identified any new issues of concern associated with GSL availability.

GSL availability is the accepted status for all current NRT products on the market; consultation on another is unlikely give any new information in relation to safety of the product.

Overall, the recommendation is that consultation is not considered necessary.

CONCLUSION

There is no reason that Nicorette Fruitfusion 6mg gum should not be classified as GSL. Because the PK profile, nicotine delivery and AE profile are commensurate with relief of urge to smoke, it may be considered that the product has a benefit to risk that is both favourable and appropriate for a GSL product, and that neither review by CHM or external consultation are required.