NICORETTE FRESHMINT 2 MG LOZENGE

PL 15513/0362

UKPAR

TABLE OF CONTENTS

Lay Summary Page 2
Scientific discussion Page 3
Steps taken for assessment Page 21
Steps taken after authorisation – summary Page 22
Summary of Product Characteristics Page 23
Product Information Leaflet Page 28
Labelling Page 32
On 9th December 2010, the MHRA granted McNeil Products Limited a Marketing Authorisation (licence) for Nicorette Freshmint 2 mg Lozenge (PL 15513/0362).

Nicorette Freshmint 2 mg Lozenge contains nicotine bitartrate dihydrate.

Nicorette Freshmint 2 mg Lozenge is a nicotine replacement therapy (NRT).

It is used to relieve and/or prevent withdrawal symptoms and reduce the cravings when trying to stop smoking or when cutting down on the number of cigarettes smoked.

Nicorette Freshmint 2 mg Lozenge can be used to completely replace all your cigarettes.

However Nicorette Freshmint 2 mg Lozenge can also be used in other ways,

- it can help cut down the number of cigarettes smoked,
- at those times when one does not want to or can’t smoke e.g.
  - To avoid harm to others e.g children or family.
  - Smoke free areas e.g Pub, work, public transport e.g aeroplanes.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Nicorette Freshmint 2 mg Lozenge outweigh the risks; hence a Marketing Authorisation has been granted.
NICORETTE FRESHMINT 2 MG LOZENGE

PL 15513/0362

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 5
Non-clinical assessment Page 8
Clinical assessment (including statistical assessment) Page 9
Overall conclusions and risk benefit assessment Page 20
INTRODUCTION

The MHRA granted a Marketing Authorisation for the medicinal product Nicorette Freshmint 2 mg Lozenge (PL 15513/0362) to McNeil Products Limited on 9th December 2012. This medicine has a General Sales Licence (GSL) and relieves and/or prevents craving and nicotine withdrawal symptoms associated with tobacco dependence. It is indicated to:

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

This application for Nicorette Freshmint 2 mg Lozenge (PL 15513/0362) is submitted as a line extension application according to Article 8.3 of Directive 2001/83/EC, cross-referring to Nicorette 2 mg Chewing Gum (PL 00022/0101), first authorised in the UK to Pharmacia Limited on 14th May 1992. This licence underwent a change of ownership (PL 00032/0248) and then another in turn on 26th April 1999 to McNeil Products Limited on 26th April 1999 (PL 15513/0169). This product contains the known active substance, nicotine bitartrate dihydrate.

It is considered that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Nicorette Freshmint 2 mg Lozenge outweigh the risks; hence this Marketing Authorisation has been granted.
**PHARMACEUTICAL ASSESSMENT**

**DRUG SUBSTANCE**

Nicotine bitartrate dihydrate  
INN: Nicotine bitartrate dihydrate  
Chemical name: Pyridine, 3-[(2S)-1-methyl-2-pyrrolidinyl]-, (2R,3R)-2,3-dihydroxybutanediolate (1:2), dihydrate  
Nicotine L- (+)-tartrate (1:2), dihydrate

**Structural formula:**

![Structural formula]

**Molecular formula:** $C_{10}H_{14}N_2*2C_4H_6O_6*2H_2O$  
**Molecular weight:** 498.4  
**Appearance:** White to off-white powder

Nicotine bitartrate dihydrate is subject to in-house specifications.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

Appropriate specifications have provided for the active substance, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Suitable Certificates of Analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be physically and chemically stable drugs, and supporting an appropriate retest period.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients in the tablet granules consist of pharmaceutical excipients mannitol (E421), xanthan gum (E415), sucralose (E955), acesulfame-K (E950), magnesium stearate (E470b) and peppermint flavour including gum arabic (E414).
With the exception of sucralose (E955) and peppermint flavour, all the ingredients in the tablet granules and the capsule shell comply with their relevant European Pharmacopoeia monographs.

Sucralose (E955) complies with the United States Pharmacopoeia. Peppermint flavour complies with in-house specifications.

None of the excipients used contain material of animal or human origin. The supplier of magnesium stearate has confirmed that it is of vegetable origin.

**Product development**
The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Satisfactory dissolution data have been provided.

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

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on commercial-scale batches of finished product and the results appear satisfactory.

**Finished product specification**
The finished product specification proposed for both release and shelf life are acceptable, and provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis for all working standards used have been provided and are satisfactory.

**Container-Closure System**
The product is packaged in blisters composed of polyvinyl chloride (PVC), polyvinylidene chloride (PVDC) and aluminium. These blisters are then packaged in an outer cardboard carton and come in pack sizes of 24 or 96 lozenges.

Specifications and Certificates of Analysis for the packaging type used have been provided. All primary product packaging complies with the European Pharmacopoeia monograph.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, with special storage conditions ‘Do not store above 25°C’. This is satisfactory.

**ADMINISTRATIVE**

**Expert Report**
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.
Summary of Product Characteristics (SmPC)
This is pharmaceutically satisfactory.

Labelling
This is pharmaceutically satisfactory.

Patient Information Leaflet (PIL)
This is pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package 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.

MAA Form
This is pharmaceutically satisfactory.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.
NON-CLINICAL ASSESSMENT

The applicant has not provided any new non-clinical studies and none are required, as this application is submitted as a line extension application according to Article 8.3 of Directive 2001/83/EC, cross-referring to Nicorette 2 mg Chewing Gum (PL 15513/0169).

The non-clinical expert report is based on literature sources and has been written by an appropriately qualified person.
INTRODUCTION
This application for Nicorette Freshmint 2 mg Lozenge (PL 15513/0362) is submitted as a line extension application according to Article 8.3 of Directive 2001/83/EC, cross-referring to Nicorette 2 mg Chewing Gum (PL 00022/0101), first authorised in the UK to Pharmacia Limited on 14th May 1992. This licence underwent a change of ownership (PL 00032/0248) and then another in turn on 26th April 1999 to McNeil Products Limited on 26th April 1999 (PL 15513/0169). This product contains the known active substance, nicotine bitartrate dihydrate.

INDICATIONS
The Applicant submitted the following indications:

Nicorette Freshmint 2mg Lozenge relieves and/or prevents craving and nicotine withdrawal symptoms associated with tobacco dependence. It is 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 Freshmint 2mg Lozenge is indicated in pregnant and lactating women making a quit attempt.

DOSE & DOSE SCHEDULE
The Applicant submitted the following dosing recommendations:

Nicorette Freshmint Lozenge is suitable for smokers who smoke 20 or fewer cigarettes per day.

*Adults and Children over 12 years of age*
Nicorette Freshmint 2mg Lozenge should be used whenever the urge to smoke is felt or to prevent cravings in situations where these are likely to occur.

Smokers willing or able to stop smoking immediately should initially replace all their cigarettes with the lozenge and as soon as they are able, reduce the number of lozenges used until they have stopped completely.

Smokers aiming to reduce cigarettes should take the lozenge, as needed, between smoking episodes to prolong smoke-free intervals and with the intention to reduce smoking as much as possible.

As soon as they are ready smokers should aim to quit smoking completely.

Most smokers require 8 to 12 lozenges per day, not to exceed 15 lozenges.

When making a quit attempt behavioural therapy, advice and support will normally improve the success rate. Those who have quit smoking, but are having difficulty discontinuing with the lozenge are recommended to contact their pharmacist or doctor for advice.
Method of administration
One lozenge should be placed in the mouth and allowed to dissolve. Periodically, the lozenge should be moved from one side of the mouth to the other, and repeated, until the lozenge is completely dissolved. You should not chew or swallow the lozenge. You should not eat or drink while a lozenge is in the mouth.

CLINICAL PHARMACOLOGY
PHARMACODYNAMICS
The pharmacological actions of nicotine bitartrate dihydrate are well known and therefore no specific studies are required.

PHARMACOKINETICS

1.1.1 Distribution
From the literature it is known that nicotine has volume of distribution of approximately 2 to 3 L/kg. Plasma protein binding of nicotine is less than 5%.

1.1.2 Metabolism
The major eliminating organ is the liver, and average plasma clearance is about 70 L/hour. The kidney and lung also metabolize nicotine. More than 20 metabolites of nicotine have been identified, all of which are believed to be less active than the parent compound.

1.1.3 Excretion
The main metabolites in the urine are cotinine (12 % of the dose) and trans-3-hydroxycotinine (37 % of the dose). Approximately 10 % of the dose is excreted unchanged in the urine. Up to 30 % may be excreted via the urine unchanged if diuresis is increased and acidification to a pH below 5.

1.1.4 Intra- and inter-individual variability
There is no information on the intra- or interindividual variability. In a classic cross-over design it is not possible to differentiate between the test and reference intrasubject variability.

1.1.5 Special pharmacokinetic considerations in target population
The pharmacokinetic studies were performed in smokers. Hence, the data on bioequivalence is representative of the pharmacokinetics in the target population.

1.1.6 Special populations

Impaired renal function
According to the applicant and previously approved summary of product characteristics, progressive severity of renal impairment is associated with a decrease in renal clearance of nicotine. Based on mean data, nicotine clearance was decreased by approximately 50% in patients with severe renal impairment. Therefore, nicotine replacement therapy (NRT) should be used with caution in patients with severe renal insufficiency.

Impaired hepatic function
The pharmacokinetics of nicotine are not affected by mild hepatic impairment, but in patients with moderate liver impairment nicotine total and non-renal clearance appears to be
decreased by 40-50%. Therefore NRT should be used with caution in patients with severe or moderate liver impairment.

**Gender**

One study on the possible pharmacokinetic difference between men and women has been performed for the nicotine transdermal patch also reported similar pharmacokinetics for both sexes.

**Race**

One study that compared the pharmacokinetics of nicotine in different races showed that cotinine levels were higher in black smokers compared to white and Latin American smokers. Another study concluded that black smokers have lower nicotine clearance than white smokers, which could in part explain the elevated concentrations of cotinine. It has been shown that nicotine clearance is similar in white and Latin American smokers. Individuals of Chinese origin, however, have been shown to have significantly lower nicotine clearance than both white and Latin American smokers.

**Weight**

In a study of the nicotine pharmacokinetics of nicotine transdermal patch, the area under curve (AUC) and $C_{\text{max}}$ of nicotine were significantly lower in obese men compared to normal-weight men after a 24 hour application of the patch. The study results provided a strong correlation between AUC and body weight and body mass index (BMI).

**Elderly**

An open, non-randomized, parallel group, single-dose study was performed to evaluate any differences in the pharmacokinetics of nicotine in healthy elderly ($\geq 65$ years of age) subjects in comparison with healthy non-elderly adults. Twenty elderly subjects and 20 healthy non-elderly adult subjects, male or female, smokers and/or snuff users, were given a single intravenous infusion of nicotine, 0.028 mg/kg over 10 minutes.

The total clearance was reduced by approximately 23 %, non-renal clearance by 21 % and renal clearance by 49 %. The total exposure was increased by 29 % compared to non-elderly adults.

**Children**

The current licensing in the UK allows NRT use in 12-17 year olds.

**Overall comments on pharmacokinetics in special populations**

There are specific warnings with respect to severe renal impairment and moderate to severe hepatic impairment. In other special populations (gender, weight, elderly) there is no need for specific dose adjustment.

Draft guideline states that pharmacokinetic and safety data are required if adolescents are included in the labelling. This may be relevant for new chemical entities (NCEs) but many published studies in which NRT has been used in adolescents reported no safety problems. The current licensing in the UK allows NRT use in 12-17 year olds.

**1.2 BIOEQUIVALENCE**

Two PK studies with the new formulation have been performed. One pivotal study and one pilot study with six different prototype formulations of the new lozenge were performed.
1) Pivotal Study

A 2 x two-way open-label cross-over, single dose, randomised study in 88 healthy subjects.

1.2.1 Test Product and reference products

<table>
<thead>
<tr>
<th>Test Products:</th>
<th>Reference Products:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: NML 2mg (lozenge)</td>
<td>C: Nicorette gum 2 mg</td>
</tr>
<tr>
<td>B: NML 4 mg (lozenge)</td>
<td>D: Nicorette gum 4 mg</td>
</tr>
</tbody>
</table>

1.2.2 Study design

The analyst and pharmacokineticist were blinded for treatment. Each period included a single dose administration of 2 or 4 mg nicotine. The lozenges were placed on the tongue and dissolved. The chewing gums were chewed for 30 minutes at a regular rate of one chew every two second, by using a metronome. Smoking was not allowed from 12 hours before and throughout each treatment. Subjects did not eat or drink from 15 minutes before and until 60 minutes after start of drug administration.

Number of subjects studied

A total of 88 healthy subject smokers were randomised. Eight subjects discontinued, due to 1 protocol violation, and 7 due to their own withdrawal of participation. 80 subjects completed the study. A total of 74 (treatment A and C) and 76 subjects were included (treatment B and D). Twelve subjects were excluded due to too high baseline nicotine levels ($\geq 5$ ng/ml), that was in accordance with the pre-specification stated in the protocol.

Doses administered (test/reference)

The new lozenge was administered as either 2 or 4 mg, compared with Nicorette gum 2 and 4 mg respectively. All subjects were to receive all four treatments.

Between-product ratios of $cC_{max}$, $cAUC_{0-t}$ and $cAUC_{0-\infty}$ were used to evaluate bioequivalence; Products were considered bioequivalent if the 90% confidence intervals (CIs) were within the bioequivalence interval (80% - 125%).

Washout period

A wash-out of 36 hours separated each treatment.

Bioequivalence was based on the corrected pharmacokinetic parameters (subtracting baseline levels of nicotine). Mean square error was used in the calculation of the 90 % confidence interval of the geometric mean ratio and bioequivalence was concluded if the interval was within 0.8-1.25 (pivotal study). In the pilot study, a 95 % confidence interval was calculated.
Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \(t_{\text{max}}\) median, range). N= 73-76. Only results for the 2 mg strength compared to 2 mg chewing gum is provided (since 4 mg is not included in the application).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>cAUC(_{0-t}) ng x h/ml</th>
<th>cAUC(_{0-\infty}) ng x h/ml</th>
<th>cC(_{\text{max}}) ng/ml</th>
<th>(t_{\text{max}}) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>11.8 (6.6)</td>
<td>14.1 (7.7)</td>
<td>3.4 (1.5)</td>
<td>1.0 (0.17-2)</td>
</tr>
<tr>
<td>Reference</td>
<td>11.2 (5.5)</td>
<td>13.2 (6.2)</td>
<td>3.8 (1.4)</td>
<td>0.75 (0.25-1.25)</td>
</tr>
</tbody>
</table>

\[*\text{Ratio (90\% CI)} = 104 (95-114)\]

\(\text{cAUC}_{0-t}\) area under the plasma concentration-time curve from time zero to \(t\) hours corrected for baseline nicotine levels
\(\text{cAUC}_{0-\infty}\) area under the plasma concentration-time curve from time zero to infinity corrected for baseline nicotine levels
\(\text{cC}_{\text{max}}\) maximum plasma concentration corrected for baseline nicotine levels
\(t_{\text{max}}\) time for maximum plasma concentration

\(*\text{ln-transformed values}^\star\)

The lower limit of the 90 % confidence interval for cC\(_{\text{max}}\) is just outside 80 %. However, given the wide therapeutic window of nicotine and wide individual titration, this is considered acceptable for the extrapolation of clinical data of the chewing gums to the lozenges.
2) Pilot study

Study design
The study was a 2 x 4 way cross-over design. Subjects were randomly assigned to one of eight treatment sequences. Three formulations with a short dissolution time (10 minutes) and three formulations with a longer dissolution time (20 minutes) were compared with the reference. Each subject was administered four formulations- three slow or three fast and the reference. The lozenges were placed on the tongue and dissolved. The chewing gums were chewed for 30 minutes at a regular rate of one chew every two second, by using a metronome. A wash-out of 36 hours separated each treatment. Blood was sampled pre-dose and up to 10 hours after administration. Smoking was not allowed from 12 hours before and throughout each treatment.

Test and reference products

<table>
<thead>
<tr>
<th>Test Products</th>
<th>Reference Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNL Short 0 mg buffer</td>
<td>Nicorette Gum</td>
</tr>
<tr>
<td>NNL Short 5 mg buffer</td>
<td></td>
</tr>
<tr>
<td>NNL Short 10 mg buffer</td>
<td></td>
</tr>
<tr>
<td>NNL Long 0 mg buffer</td>
<td></td>
</tr>
<tr>
<td>NNL Long 5 mg buffer</td>
<td></td>
</tr>
<tr>
<td>NNL Long 10 mg buffer</td>
<td></td>
</tr>
</tbody>
</table>

Population studied
A total of 45 healthy smoking subjects were screened and 40 included in the study. One subject discontinued due to other reason. There were in total 4 subjects with baseline nicotine levels $\geq 5$ ng/ml at one or two of the treatment sessions. Valid periods of these subjects were included in the pharmacokinetic analysis.

Results

Table 8: Mean pharmacokinetic parameters for prototypes with short dissolution time (mean±SD, n=18-20).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$C_{\text{max}}$ (ng/mL)</th>
<th>$t_{\text{max}}$ (min)</th>
<th>$\text{AUC}_t$ (ng/mLxh)</th>
<th>$\text{AUC}_{\infty}$ (ng/mLxh)</th>
<th>$t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNL Short 0 mg</td>
<td>3.7±0.9</td>
<td>45</td>
<td>12.2±5.2</td>
<td>15.0±6.7</td>
<td>3.5±1.1</td>
</tr>
<tr>
<td>NNL Short 5 mg</td>
<td>5.1±1.2</td>
<td>30</td>
<td>14.2±5.2</td>
<td>16.7±6.4</td>
<td>2.9±1.1</td>
</tr>
<tr>
<td>NNL Short 10 mg</td>
<td>5.3±1.8</td>
<td>20</td>
<td>15.7±6.8</td>
<td>18.8±7.7</td>
<td>3.0±0.94</td>
</tr>
<tr>
<td>NICORETTE® Gum</td>
<td>4.7±1.6</td>
<td>30</td>
<td>13.1±4.0</td>
<td>15.6±4.7</td>
<td>3.2±0.83</td>
</tr>
</tbody>
</table>
Table 9: Mean pharmacokinetic parameters for prototypes with long dissolution time (mean±SD, n=18-20).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$C_{\text{max}}$ (ng/mL)</th>
<th>$t_{\text{max}}$ (min)</th>
<th>$\text{AUC}_{t}$ (ng/mLxh)</th>
<th>$\text{AUC}_{\infty}$ (ng/mLxh)</th>
<th>$t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNL Long 0 mg</td>
<td>4.3±1.9</td>
<td>60</td>
<td>12.3±5.1</td>
<td>14.8±5.7</td>
<td>3.3±0.96</td>
</tr>
<tr>
<td>NNL Long 5 mg</td>
<td>5.1±1.0</td>
<td>60</td>
<td>14.4±3.2</td>
<td>16.9±3.8</td>
<td>3.2±0.92</td>
</tr>
<tr>
<td>NNL Long 10 mg</td>
<td>5.8±2.6</td>
<td>45</td>
<td>15.7±4.3</td>
<td>18.3±5.1</td>
<td>3.1±1.3</td>
</tr>
<tr>
<td>NICORETTE® Gum</td>
<td>4.7±1.9</td>
<td>30</td>
<td>11.9±5.2</td>
<td>14.0±5.4</td>
<td>2.8±0.88</td>
</tr>
</tbody>
</table>

Based on the bioequivalence determinations of the ones with short dissolution times, the formulations most similar to Nicorette was the one with 5 mg buffer.

Of the formulations with long dissolution time, the formulation without buffer (NNL Long 0 mg) was the one most similar to Nicorette 2 mg gum.

1.2.3 Conclusion on Bioequivalence

The Applicant has submitted the results of two studies conducted with the new formulation. The pilot study investigated six different formulations showing that two of them were most similar to Nicorette chewing gum 2 mg.

The formulation intended for marketing was the one tested in the pivotal bioequivalence study. Bioequivalence was shown with respect to extent of absorption between Nicorette lozenge 2 mg and Nicorette chewing gum 2 mg.

The lower limit of $C_{\text{max}}$ was just below the limit (79%) therefore bioequivalence was not shown.

The difference of the pharmacokinetic (PK) profile (ONS vs reference products) is expected to be of little clinical significance for a product which is self-titrated to a subject’s needs by frequency of dosing.

Efficacy

In this application, no specific study has been performed to assess the efficacy of the Nicorette Freshmint 2 mg Lozenge. Instead, extrapolation of efficacy and safety data from Nicorette chewing gum 2 mg to Nicorette lozenge 2 mg is made based on pharmacokinetic data.

As described above, bioequivalence was shown with respect to extent of absorption between Nicorette lozenge 2 mg and Nicorette chewing gum 2 mg. Regarding rate of absorption ($C_{\text{max}}$) strict bioequivalence was not shown, however, borderline to the limits of 80-125 % (being 79-93%). Median $T_{\text{max}}$ for Nicorette lozenge 2 mg was 1 hour while it was 0.75 hours for Nicorette chewing gum 2 mg. Thus, the pharmacokinetic data show a slightly different pharmacokinetic profile for the lozenge compared with the gum.

However, the effects of nicotine are well-known and there are several nicotine products available on the market with different pharmacokinetic profiles.
The difference of PK profile (ONS vs reference products) is expected to be of little clinical significance for a product which is self-titrated to a subject’s needs by frequency of dosing.

OVERALL CONCLUSIONS ON CLINICAL EFFICACY
In this application, no specific study has been performed to assess the efficacy of the 2 mg Nicorette lozenge. Instead, extrapolation of efficacy and safety data from Nicorette chewing gum 2 mg to Nicorette lozenge 2 mg is made based on pharmacokinetic data.

Clinical data has been published worldwide over the past 20 years on the efficacy of nicotine gum in controlling tobacco withdrawal symptoms and the efficacy of nicotine gum in long-term smoking cessation. Meta-analyses of this data show that nicotine gum significantly increases long-term abstinence rates compared to either placebo or no treatment.

The efficacy of Nicorette Gum 2 mg in stopping smoking has been investigated in several double-blind, randomized, placebo-controlled trials. In these studies, statistically significant effects on abstinence rates in favour of Nicorette Gum were observed vs. placebo.

As described above, bioequivalence was shown with respect to extent of absorption between Nicorette lozenge 2 mg and Nicorette chewing gum 2 mg. Regarding rate of absorption ($C_{\text{max}}$) strict bioequivalence was not shown, however, borderline to the limits of 80-125 % (being 79-93%).

The effects of nicotine are well-known and there are several nicotine products available on the market with different pharmacokinetic profiles. Based on the wide therapeutic window and the possibility for individual titration, the small difference in pharmacokinetic profile is not considered to constitute a problem and specific efficacy studies for Nicorette lozenge 2 mg are not necessary.

SAFETY
A large number of different nicotine replacement therapy products are available and the overall safety profile of nicotine is well-known. These products are individually titrated. Based on the pharmacokinetic data for the Nicorette lozenge, the exposure to nicotine will not be higher with this product. No long-term safety data are available with this product.

Adverse events
All adverse events (AEs) reported for Nicorette lozenge 2 mg and Nicorette Gum 2 mg are listed in the table below. The most common AEs observed with both formulations were related to the gastrointestinal tract, with nausea being the most frequently reported AE. The majority of AEs were mild or moderate in severity.
Overview of treatment-related adverse events reported in single-dose studies with new NML 2 mg and comparator, Nicorette Gum 2 mg

<table>
<thead>
<tr>
<th>System organ class Preferred term</th>
<th>Pilot Study</th>
<th>Pivotal bioequivalence Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NNL 2 mg long 0 mg* (n=20)</td>
<td>Nicorette Gum 2 mg (n=20)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gastritis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Odynophagia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoaesthesia oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal discomfort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorder and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling cold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensation of foreign body</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

*Note: The prototype formulation NNL 2 mg long 0 mg used in the Pilot Study is the same formulation as the NML 2 mg used in the pivotal Study.

In the Pivotal Study, 4 mg strengths were also studied and higher incidences of AEs were reported after this dose (25 AEs for Nicorette lozenge 4 mg and 40 AEs for Nicorette Gum 4 mg), with nausea most frequently reported.

In the Pilot Study, other prototype formulations were also studied. Two severe treatment-related AEs were reported with the formulation called “NNL Short with 10 mg buffer” (respiratory distress and sensation of foreign body).

No deaths or serious AEs were reported during the study. The type and number of AEs reported were similar between the test and the reference product in the two pharmacokinetic studies. Most AEs were from the GI tract, e.g. nausea, which is commonly observed for nicotine products.
1.3 LOCAL SAFETY
One case of local irritation in the mouth or throat (oropharyngeal discomfort) with the Nicorette lozenge 2 mg was reported during the Pivotal Study. Odynophagia was reported by one subject in the Nicorette lozenge group and one subject in the Nicorette Gum group reported oral hypoaesthesia.

Based on these limited data, no signs of significant local safety problems with the new formulation have emerged. The overall safety profile of nicotine products is well-known as a large number of nicotine replacement products are available. The product is generally well tolerated. No non-clinical local tolerance studies are available.

No new excipients are included in this formulation. This product contains nicotine as nicotine bitartrate dihydrate and this salt is also used in other NRT products with the same route of administration. Hence, although no long-term safety data are available for this product, it seems reasonable to conclude that the safety would not differ from other NRT products.

1.4 DISCONTINUATION DUE TO AES
No subjects were reported as discontinued because of AEs.

1.5 POST MARKETING EXPERIENCE
The product has not been marketed; hence, there is no post marketing experience.

1.6 PROPOSALS FOR POST MARKETING SURVEILLANCE / STUDIES
No specific post authorisation follow-up activities are required other than regular periodic safety update report (PSUR) submissions.

OVERALL CONCLUSIONS ON CLINICAL SAFETY
The clinical efficacy, safety and pharmacology of the active ingredient nicotine are already well-established and documented. This application contains an adequate review of clinical data.

From a clinical point of view the risk-benefit is considered positive therefore, the current application could be considered approvable.

EXPERT REPORTS
The clinical expert report has been written by a suitably qualified person and contains 31 literature references up to 2008. This is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
These are satisfactory.

APPLICATION FORMS (MAA)
This is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
This is satisfactory.
MEDICAL CONCLUSION
The grant of a Marketing Authorisation is recommended for this application.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Nicorette Freshmint 2 mg Lozenges are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
In this application, no specific study has been performed to assess the efficacy of the Nicorette Freshmint 2 mg Lozenge. Instead, extrapolation of efficacy and safety data from Nicorette chewing gum 2 mg to Nicorette lozenge 2 mg is made based on pharmacokinetic data. This is satisfactory.

The SmPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical and clinical concerns have been identified. Extensive clinical experience with nicotine bitartrate dihydrate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
**NICORETTE FRESHMINT 2 MG LOZENGE**

**PL 15513/0362**

**STEPS TAKEN FOR ASSESSMENT**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation applications on 25(^{th}) November 2009.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 14(^{th}) December 2009.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application further information was requested regarding the quality section of the dossier on 19(^{th}) May 2010 and 28(^{th}) July 2010. Following assessment of the application further information was requested regarding the clinical section of the dossier on 7(^{th}) June 2010.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 14(^{th}) July 2010 and 25(^{th}) October 2010 for the quality section. The applicant responded to the MHRA’s requests, providing further information on 8(^{th}) July 2010 for the clinical section.</td>
</tr>
<tr>
<td>5</td>
<td>The applications were determined on 9(^{th}) December 2010.</td>
</tr>
</tbody>
</table>
NICORETTE FRESHMINT 2 MG LOZENGE

PL 15513/0362

STEPS TAKEN AFTER ASSESSMENT

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Nicorette Freshmint 2 mg Lozenge.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each lozenge contains 2 mg nicotine (as nicotine bitartrate dihydrate).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Compressed lozenge.

White to off white, oval, with mint flavour, one side marked with a 3-sided figure containing the letter “n”.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Nicorette Freshmint 2mg Lozenge relieves and/or prevents craving and nicotine withdrawal symptoms associated with tobacco dependence. It is 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 Freshmint 2mg Lozenge is indicated in pregnant and lactating women making a quit attempt.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Nicorette Freshmint Lozenge is suitable for smokers who smoke 20 or fewer cigarettes per day.

Adults and Children over 12 years of age
Nicorette Freshmint 2mg Lozenge should be used whenever the urge to smoke is felt or to prevent cravings in situations where these are likely to occur.

Smokers willing or able to stop smoking immediately should initially replace all their cigarettes with the lozenge and as soon as they are able, reduce the number of lozenges used until they have stopped completely.

Smokers aiming to reduce cigarettes should take the lozenge, as needed, between smoking episodes to prolong smoke-free intervals and with the intention to reduce smoking as much as possible.

As soon as they are ready smokers should aim to quit smoking completely.

Most smokers require 8 to 12 lozenges per day, not to exceed 15 lozenges.

When making a quit attempt behavioural therapy, advice and support will normally improve the success rate. Those who have quit smoking, but are having difficulty discontinuing with the lozenge are recommended to contact their pharmacist or doctor for advice.

Method of administration
One lozenge should be placed in the mouth and allowed to dissolve. Periodically, the lozenge should be moved from one side of the mouth to the other, and repeated, until the lozenge is completely dissolved. You should not chew or swallow the lozenge. You should not eat or drink while a lozenge is in the mouth.

4.3 CONTRAINDICATIONS
Hypersensitivity to any of components of the lozenge.
Nicorette Freshmint Lozenge is contraindicated in children under the age of 12 years.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Any risks which may be associated with the use of NRT are substantially outweighed in virtually all circumstances by the well established dangers of continued smoking.
Underlying cardiovascular disease: In stable cardiovascular disease Nicorette Freshmint Lozenge presents a lesser hazard than continuing to smoke. However dependent smokers currently hospitalised as a result of myocardial infarction, severe dysrhythmia or cerebrovascular accident and who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions. If this fails, Nicorette Freshmint Lozenge may be considered, but as data on safety in this patient group are limited, initiation should only be under medical supervision.

Diabetes Mellitus. Patients with diabetes mellitus should be advised to monitor their blood sugar levels more closely than usual when NRT is initiated as catecholamines released by nicotine can affect carbohydrate metabolism.

Allergic reactions: susceptibility to angioedema and urticaria.

Renal and hepatic impairment: Use with caution in patients with moderate to severe hepatic impairment and/or severe renal impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse effects.

Phaeochromocytoma and uncontrolled hyperthyroidism: Use with caution in patients with uncontrolled hyperthyroidism or phaeochromocytoma as nicotine causes release of catecholamines.

Gastrointestinal Disease: Swallowed nicotine may exacerbate symptoms in patients suffering from oesophagitis, gastric or peptic ulcers and oral NRT preparations should be used with caution in these conditions. Ulcerative stomatitis has been reported.

Danger in small children: Doses of nicotine tolerated by adult and adolescent smokers can produce severe toxicity in small children that may be fatal. Products containing nicotine should not be left where they may be misused, handled or ingested by children, see section 4.9 Overdose.

Transferred dependence: Transferred dependence is rare and is both less harmful and easier to break than smoking dependence.

Stopping smoking: Polycyclic aromatic hydrocarbons in tobacco smoke induce the metabolism of drugs metabolised by CYP 1A2 (and possibly by CYP 1A1). When a smoker stops smoking, this may result in slower metabolism and a consequent rise in blood levels of such drugs. This is of potential clinical importance for products with a narrow therapeutic window, e.g. theophylline, clozapine and ropinirole.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
No clinically relevant interactions between nicotine replacement therapy and other drugs have definitely been established. However nicotine may possibly enhance the haemodynamic effects of adenosine i.e. increase in blood pressure and heart rate and also increase pain response (angina-pectoris type chest pain) provoked by adenosine administration.

4.6 PREGNANCY AND LACTATION

Pregnancy
Stopping smoking is the single most effective intervention for improving the health of both the pregnant smoker and her baby, and the earlier abstinence is achieved the better. Ideally smoking cessation during pregnancy should be achieved without NRT. However, if the mother cannot (or is considered unlikely to) quit without pharmacological support, NRT may be used as the risk to the foetus is lower than that expected with smoking tobacco. Stopping completely is by far the best option but if this is not achievable Nicorette Freshmint 2mg Lozenge may be used in pregnancy as a safer alternative to smoking. Because of the potential for nicotine-free periods, intermittent dose forms are preferable, but patches may be necessary if there is significant nausea and/or vomiting. If patches are used they should, if possible, be removed at night when the foetus would not normally be exposed to nicotine.
Lactation
The relatively small amounts of nicotine found in breast milk during NRT use are less hazardous to the infant than second-hand smoke. Intermittent dose forms would minimize the amount of nicotine in breast milk and permit feeding when levels were at their lowest.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Not applicable.

4.8 UNDESIRABLE EFFECTS
Nicorette Freshmint Lozenge may cause adverse reactions similar to those associated with nicotine given by other means, including smoking, and these are mainly dose-dependent. At recommended doses Nicorette Freshmint Lozenge has not been found to cause any serious adverse effects. Excessive consumption of Nicorette Freshmint Lozenge by those who have not been in the habit of inhaling tobacco smoke could possibly lead to nausea, faintness or headaches.

Some symptoms may be related to nicotine withdrawal associated with stopping smoking. These can include: irritability/aggression, dysphoria/depressed mood, anxiety, restlessness, poor concentration, increased appetite/weight gain, urges to smoke (cravings), night-time awakenings/sleep disturbance and decreased heart rate.

Increased frequency of aphthous ulcer may occur after stopping smoking. The causality is unclear.

Most of the undesirable effects reported by the patient occur during the first 3-4 weeks after start of treatment. During the first few days of treatment irritation in the mouth and throat may be experienced. Most patients will get used to this sensation after the first few days.

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/10 000, <1/100); rare (≥1/10 000, <1/10 000); very rare (<1/10 000); not known (cannot be estimated from the available data).

Nervous system disorders:
Common: Dizziness, headache.

Gastrointestinal disorders:
Common: Nausea, gastrointestinal discomfort, hiccups

General disorders and administration site conditions:
Common: Sore mouth or throat, salivary hypersecretion
Rare: Allergic reactions including angioedema

Respiratory, thoracic and mediastinal disorders:
Common: Coughing

Cardiac disorders:
Common: Palpitations
Rare: Reversible atrial fibrillation

Skin and subcutaneous tissue disorders:
Uncommon: Erythema, urticaria

4.9 OVERDOSE
Symptoms: The minimum lethal dose of nicotine in a non-tolerant man has been estimated to be 40 to 60 mg. Symptoms of acute nicotine poisoning include nausea, salivation, abdominal pain, diarrhea, sweating, headache, dizziness, disturbed hearing and marked weakness. In extreme cases, these symptoms may be followed by hypotension, rapid or weak or irregular pulse, breathing difficulties, prostration, circulatory collapse and terminal convulsions.
Management of an overdose: All nicotine intake should stop immediately and the patient should be treated symptomatically. Artificial respiration should be instituted if necessary. Activated charcoal reduces the gastro-intestinal absorption of nicotine.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Drug used in nicotine dependence.
Nicotine is an agonist at nicotine receptors in the peripheral and central nervous system and has pronounced CNS and cardiovascular effects. Abrupt cessation of the use of tobacco-containing products following a prolonged period of daily use results in a characteristic withdrawal syndrome that includes four or more of the following: dysphoria or depressed mood; insomnia; irritability, frustration or anger; anxiety; difficulty concentrating, restlessness or impatience; decreased heart rate; and increased appetite or weight gain. Nicotine craving is an important element in the withdrawal syndrome after smoking cessation. Clinical studies have shown that nicotine replacement products can help smokers abstain from smoking by relieving these withdrawal symptoms. Increased appetite is a recognised symptom of nicotine withdrawal and post-cessation weight gain is common. Clinical trials have demonstrated that Nicotine Replacement Therapy can help control weight following a quit attempt.

### 5.2 Pharmacokinetic Properties

**Absorption**
The amount of nicotine released from a nicotine lozenge that is absorbed depends on the amount of nicotine released in the oral cavity and the amount thereof that is swallowed. Most of the nicotine released in the oral cavity is absorbed through the oral mucosa. Systemic bioavailability of swallowed nicotine is lowered due to first-pass metabolism. A maximum nicotine plasma concentration of 3-4 ng/mL is achieved after a single dose of the 2 mg lozenge. The total nicotine intake during the day (indicated by \( \text{AUC}_{\infty} \)) is at least as much as that provided from the Nicorette® Gum 2 mg. \( \text{AUC}_{\infty} \) after one single dose of 2 mg lozenge is between 14 and 15 ng/mLxh.

**Distribution**
The volume of distribution following intravenous administration of nicotine is about 2 to 3 l/kg. Plasma protein binding of nicotine is less than 5%. Therefore, changes in nicotine binding from use of concomitant drugs or alterations of plasma proteins by disease states would not be expected to have any significant effects on the nicotine pharmacokinetics.

**Biotransformation**
The average plasma clearance of nicotine is about 70 l/hour and the half-life is approximately 2-3 hours.

**Renal Impairment**
Progressive severity of renal impairment is associated with decreased total clearance of nicotine. Nicotine clearance was decreased by 50% on average in subjects with severe renal impairment. Raised nicotine levels have been seen in smokers undergoing haemodialysis.

**Hepatic Impairment**
The pharmacokinetics of nicotine is unaffected in cirrhotic users with mild liver impairment (Child-Pugh score 5) and decreased by 40-50% in cirrhotic users with moderate liver impairment (Child-Pugh score 7). There is no information available in subjects with a Child-Pugh score > 7. A minor reduction in total clearance of nicotine has been demonstrated in healthy elderly users, however this does not justify adjustment of dosage.

**Metabolism**
The major eliminating organ is the liver, although the kidney and lung also metabolise nicotine. More than 20 metabolites of nicotine have been identified, all of which are believed to be less active than the parent compound. The primary metabolite of nicotine in plasma, cotinine, has a half-life of 15 to 20 hours and concentrations that exceed nicotine by 10-fold.

**Excretion**
The primary urinary metabolites are cotinine (12% of the dose) and trans-3-hydroxy-cotinine (37% of the dose). About 10% of nicotine is excreted unchanged in the urine. As much as 30% of nicotine may be excreted unchanged in the urine with high flow rates and acidification of the urine below pH 5.
5.3 PRECLINICAL SAFETY DATA
Preclinical data indicate that nicotine is neither mutagenic nor genotoxic.
There are no other findings derived from preclinical testing of relevance to the prescriber in
determining the safety of the product which have not been considered in other relevant sections of
this Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Mannitol (E421)
Xanthan gum (E415)
Sucralose (E955)
Acesulfame-K (E950)
Magnesium stearate (E470b)
Peppermint Flavour including Gum Arabic (E414)

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER
Pack sizes:
Aluminium/polyvinylidenechloride/polyvinylchloride blister containing 12 lozenges. Cardboard
boxes in pack sizes of 24 or 96 lozenges.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORITY HOLDING
McNeil Products Limited
Foundation Park
Roxborough Way
Maidenhead
Berkshire SL6 3UG
United Kingdom

8 MARKETING AUTHORITY NUMBER(S)
PL 15513/0362

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
09/12/2010

10 DATE OF REVISION OF THE TEXT
09/12/2010
Details of Nicorette ActiveStop are at the end of this leaflet.

What does nicorette freshmint 2mg lozenge do?
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 use nicorette freshmint 2mg lozenge, nicotine is released and passes into your body through the lining of your mouth. The nicotine released is sufficient to relieve the unpleasant nicotine withdrawal symptoms. It will also help to stop your craving to smoke but will not give you the “buzz” you get from smoking a cigarette.

Benefits you can get from using NRT instead of smoking
For the best effect, ensure that you use nicorette freshmint 2mg lozenge correctly – see “How to Use Nicorette Freshmint 2mg Lozenge”.

The benefits of stopping smoking far outweigh any potential risk from using nicotine from NRT. It is the toxins in cigarette smoke such as tar, lead, cyanide and ammonia that cause smoking related disease and death, not the nicotine.

- You may think that smoking helps relieve feelings of anxiety and stress, but it does not deal with the cause of stress and leads to a number of serious diseases. In addition, the feeling of relaxation after smoking is temporary, with withdrawal symptoms and cravings soon returning. Nicotine replacement therapy can help relieve nicotine withdrawal symptoms such as irritability, low mood, anxiety, restlessness and cravings when used in place of cigarettes.

- NRT may benefit smokers who want to quit, by helping to control weight gain that may be experienced when trying to stop smoking. Use of NRT is safer than smoking tobacco but as soon as you are ready, you should aim to stop smoking completely.

1 What this medicine is for
Nicorette freshmint 2mg lozenge is a nicotine replacement therapy (NRT).
It is used to relieve and/or prevent withdrawal symptoms and reduce the cravings you get when you try to stop smoking or when cutting down the number of cigarettes you smoke.

Ideally you should always aim to stop smoking. You can use nicorette freshmint 2mg lozenge to achieve this by using it to completely replace all your cigarettes. However nicorette freshmint 2mg lozenge can also be used in other ways,
- if you feel unable to stop smoking completely, or wish to replace certain cigarettes and therefore it can help you to cut down the number of cigarettes you smoke,
- at those times when you can’t or do not want to smoke. For example,
  - Where you don’t want to smoke and avoid harm to others e.g children or family,
  - Smoke free areas e.g Pub, work, public transport e.g aeroplanes.

It may also help increase your motivation to quit. When making a quit attempt a behavioural support programme will increase your chances of success.
Before using this medicine

Do not use Nicorette Freshmint 2mg Lozenge:
- if you have an allergy to nicotine or any of the other ingredients.
- if you are a child under 12 years of age.

Talk to your doctor, nurse or pharmacist...
- If you are pregnant or breast-feeding – you may be able to use nicotine replacement therapy (NRT) to help you give up smoking but you should try to give up without it. See "If you are pregnant or breast-feeding" section.
- if you are in hospital because of heart disease (including heart attack, disorders of heart rate or rhythm, or stroke).
- In other heart conditions not requiring you to be in hospital, using NRT is better than continuing to smoke.
- if you have a stomach ulcer, duodenal ulcer, inflammation of the stomach or inflammation of the oesophagus (passage between the mouth and stomach).
- if you have liver or kidney disease.
- if you have an overactive thyroid gland or have a phaeochromocytoma (a tumour of the adrenal gland that can affect blood pressure) – your doctor will have told you this.
- if you have diabetes – monitor your blood sugar levels more often when starting to use nicorette freshmint 2mg lozenge as you may find your insulin or medication requirements alter.
- if you are taking any other medicines such as theophylline, clozapine or ropinirole. Stopping smoking may require the dose of these medicines to be adjusted.

If any of these applies, talk to your doctor, nurse or pharmacist.

If you are pregnant or breast-feeding

If you are pregnant:
1) Firstly, you should try to give up smoking without NRT. Stopping completely is by far the best option. The earlier and quicker you do this the better it is for you and your baby.

2) Secondly, if you can't manage this, you can use NRT as a safer alternative to smoking as the risks to your baby are far less than smoking, however you should talk to your doctor, nurse or pharmacist for advice.

Products that are used intermittently, including nicorette freshmint 2mg lozenge, may be preferable to nicotine patches. However, patches may be more suitable if you have nausea or sickness. If you do use patches take them off before going to bed at night.

If you are breast-feeding:
1) Firstly, you should try to give up smoking without NRT.

2) Secondly, if you can't manage this you are best to use NRT products that are taken intermittently (not patches), however you should talk to your doctor, nurse or pharmacist for advice. Breast-feed just before you use nicorette lozenge to ensure that the baby gets the smallest amount of nicotine possible.

If you do need to use NRT to help you quit, the amount of nicotine that the baby may receive is considerably smaller and less harmful than the second-hand smoke they would inhale if you smoked. Tobacco smoke produces breathing and other problems in babies and children.

How and when to use this medicine

How to use Nicorette Freshmint 2mg Lozenge

Place the lozenge in the mouth. Allow it to slowly dissolve. This will release nicotine, which you will absorb through the lining of your mouth. Nicorette freshmint 2mg lozenge should NOT be chewed or swallowed. You should not eat or drink while a lozenge is in the mouth.

The number of lozenges you use each day will depend on how many cigarettes you smoked and how strong they were. See dosing information over the page to find out the dose you should use.
When to use Nicorette Freshmint 2mg Lozenge

If you smoke 20 or fewer cigarettes a day, the 2 mg nicotine lozenge will help relieve your cravings.

If you are able to stop smoking you should use the lozenge, when needed, in place of cigarettes. As soon as you can (this could be after a number of weeks or months) you should reduce the number of lozenges until you have stopped using them completely.

If you are unable to stop smoking or do not feel ready to quit at this time, you should replace as many cigarettes as possible with the lozenge. There are toxins in cigarettes that can cause harm to your body. Nicorette freshmint 2mg lozenge provides a safer alternative to smoking, for both you and those around you. Reducing the amount of cigarettes may also help you to become more motivated to stop smoking. As soon as you are ready you should aim to stop smoking completely.

You can also use the lozenge on those occasions when you can’t or don’t want to smoke e.g. social situations such as a party, in the pub or when at work.

When making a quit attempt behavioural therapy, advice and support will normally improve the success rate. If you have quit smoking and want to stop using nicotine freshmint 2mg lozenge but are finding this difficult you should contact your doctor, nurse or pharmacist for advice.

Below is the dosage information for the nicorette freshmint 2mg lozenge. This shows the number of lozenges you should be using, when you should take them, how you should take them and the maximum amount of time you should be using Nicotine Replacement Therapy (NRT) for.

Children under 12 years

Do not give this product to children under 12 years.

Adults and children aged 12 years and over

<table>
<thead>
<tr>
<th>Age</th>
<th>Dosage of lozenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults and children aged 12 years and over</td>
<td>One lozenge to be taken as required to relieve cravings.</td>
</tr>
</tbody>
</table>

- Most people take between 8 to 12 lozenges per day.
- Do not take more than 15 lozenges per day.
- Do not exceed the stated dose.

If you have used too much Nicorette Freshmint 2mg Lozenge

If you have used more than the recommended amount of nicorette freshmint 2mg lozenge you may experience nausea (feeling sick), salivation, pain in your abdomen, diarrhoea, sweating, headache, dizziness, hearing disturbance or weakness.

- If you do any of these effects contact a doctor or your nearest hospital Accident and Emergency department immediately. Take this leaflet and the pack with you.

If a child has used or swallowed a Nicorette Freshmint 2mg lozenge

- Contact a doctor or your nearest hospital Accident and Emergency department immediately if a child under 12 years uses, chews or swallows this medicine. Take this leaflet and the pack with you.

Nicotine ingestion by a child may result in severe poisoning.

Possible side-effects

Like all medicines, nicorette freshmint 2mg lozenge can have side-effects. As many of the effects are due to nicotine, they can also occur when nicotine is obtained by smoking.

Effects related to stopping smoking (nicotine withdrawal)

You may experience unwanted effects because by stopping smoking you have reduced the amount of nicotine you are taking. You may also experience these effects if you under use nicorette freshmint 2mg lozenge before you are ready to reduce your nicotine intake.

- irritability or aggression
- feeling low
- anxiety
- restlessness
- poor concentration
- increased appetite or weight gain
- urges to smoke (craving)
- night time awakening or sleep disturbance
- lowering of heart rate
UKPAR Nicorette Freshmint 2 mg Lozenge

Effects of too much nicotine
You may also get these effects if you are not used to inhaling tobacco smoke.

⚠ These effects include:
- feeling faint
- feeling sick (nausea)
- headache

Side-effects for Nicorette Freshmint 2mg Lozenge

Common side-effects:
(less than 1 in every 10 people are affected)
- dizziness
- headache
- feeling sick (nausea)
- stomach discomfort
- hiccups
- sore mouth or throat
- coughing
- chest palpitations
- increased salivation

Uncommon side-effects
(less than 1 in every 100 people are affected)
- redness or itching of the skin
- hives (urticaria)

Rare side-effects:
(less than 1 in 1,000 people are affected)
- abnormal beating of the heart
- allergic reactions (swelling of the mouth, lips, throat and tongue, itching of the skin, swelling of skin, ulceration and inflammation of the lining of the mouth).

➤ If you notice these or any other unwanted effects not listed in this leaflet tell your doctor, nurse or pharmacist.
➤ When you stop smoking you may also develop mouth ulcers. The reason why this happens is unknown.

5 Storing and disposal
- Keep nicorette freshmint 2mg lozenge out of the reach and sight of children and animals. Nicotine in high doses can be very dangerous and sometimes fatal if taken by small children.
- Do not store nicorette freshmint 2mg lozenge above 25°C.

Do not use the product after the ‘Use before’ date on the box or blister strip.

Dispose of lozenges sensibly away from children and animals. Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 Further information

What’s in this medicine?
The active ingredient is nicotine. Each lozenge contains 2 milligrams of nicotine (as nicotine bitartrate dihydrate).

Other ingredients are: Mannitol (E421), Xanthan gum (E415), Sucralose (E955), Acesulfame potassium (E950), Magnesium stearate (E470b), Peppermint Flavour including Gum Arabic (E414).

What the medicine looks like
Nicorette freshmint 2mg lozenge is white to off white, oval, with a mint flavour.

The lozenges are blister packed in sheets of 12 and supplied in packs of 24 or 96 lozenges. Not all pack sizes may be marketed.

Who makes Nicorette Freshmint 2mg Lozenge?
The Product Licence holder is McNeil Products Ltd, Maidenhead, Berkshire, SL6 3UG, UK.
The manufacturer is McNeil AB, Helsingborg, Sweden.

This leaflet was prepared in September 2010 ©.

Information about Nicorette ActiveStop
Nicorette ActiveStop is a personalised support programme which works with Nicorette to support you, with the aim of helping you give up smoking. All you need is internet access and a mobile telephone.
Call 0800 244 838 for information.
Use: This product strength is suitable for those smoking 20+ cigarettes or fewer a day. Nicorette freshmint 2mg lozenge is used to relieve and/or prevent withdrawal symptoms and reduce the craving you get when you try to stop smoking or when cutting down the number of cigarettes you smoke. It provides a safer alternative to smoking for both the individual and those around them. Ideally you should aim to stop smoking. However, nicorette freshmint 2mg lozenge can be used in a number of different ways, 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 cut down the number of cigarettes you smoke. It may also help increase your motivation to quit.

Directions: For adults and children aged 12 years and over. Do not chew or swallow the lozenge. Place the lozenge in your mouth and allow to dissolve. Stop 1 lozenge when required, usually 8-12 lozenges per day. Do not take more than 16 lozenges per day.

Read the information leaflet carefully before use.

Warning: Do not exceed the stated dose

If you are pregnant, talk to your doctor, pharmacist or nurse for advice before using this product. If you need any advice before starting to use this product, talk to your doctor, pharmacist or nurse. 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 24 compressed lozenges, each containing 2mg nicotine. Other ingredients are E421, E415, E950, E950, E470c and E414.

Storage: Keep out of reach and sight of children. Do not store above 30°C. Dispose of sensibly. Please read the enclosed leaflet for instructions.

Use before: 818995

Batch No.