

**NICORETTE QUICKMIST 1MG/SPRAY MOUTHSPRAY  
PL 15513/0357  
(NICOTINE)**

**UKPAR**

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**NICORETTE QUICKMIST 1MG/SPRAY MOUTHSPRAY  
PL 15513/0357**

**LAY SUMMARY**

On 30<sup>th</sup> November 2010, the MHRA granted McNeil Products Limited a Marketing Authorisation (licence) for Nicorette QuickMist 1mg/spray mouthspray.

Nicorette QuickMist 1mg/spray mouthspray contains the active ingredient nicotine.

Nicorette QuickMist 1mg/spray mouthspray 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 QuickMist 1mg/spray mouthspray can be used to completely replace all your cigarettes.

However Nicorette QuickMist 1mg/spray mouthspray 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 QuickMist 1mg/spray mouthspray outweigh the risks; hence a Marketing Authorisation has been granted.

**NICORETTE QUICKMIST 1MG/SPRAY MOUTHSPRAY  
PL 15513/0357**

**SCIENTIFIC DISCUSSION**

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## INTRODUCTION

The UK granted a Marketing Authorisation for the medicinal product Nicorette QuickMist 1mg/spray mouthspray (PL 15513/0357) to McNeil Products Limited on 30<sup>th</sup> November 2010. This, a General Sales List (GSL) medicine 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 QuickMist 1mg/spray mouthspray is submitted under Article 8.3 of Directive 2001/83/EC as amended, as a line extension of the applicant's approved product, Nicorette Nasal Spray 10mg/ml. Nicorette Nasal Spray 10mg/ml was initially authorised to Pharmacia Laboratories Limited on 17<sup>th</sup> May 1994 (PL 00022/0141) and then underwent a change of ownership to Pharmacia Limited on 30<sup>th</sup> August 1999 (PL 00032/0255). This, in turn, underwent a change of ownership to McNeil Products Limited on 1<sup>st</sup> February 2008 (PL 15513/0180).

A reclassification application to change Nicorette QuickMist 1mg/spray mouthspray from a Pharmacy (P) to General Sales List (GSL) medicine was submitted in parallel and was assessed separately to the Marketing Authorisation Application (MAA). The assessment of the reclassification can be found at the end of this report (Annex I).

Nicotine is an agonist at nicotine receptors in the peripheral and central nervous system (CNS) and has pronounced CNS and cardiovascular effects.

The pharmacovigilance system as described by the applicant fulfils the requirements and also 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.

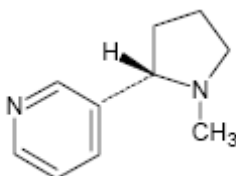
The Marketing Authorisation Holder (MAH) has provided a Risk Management Plan (RMP) that proposes no product specific surveillance activities beyond routine surveillance be undertaken. This is satisfactory.

## PHARMACEUTICAL ASSESSMENT

### DRUG SUBSTANCE

#### Nicotine

INN: Nicotine  
Chemical name: 3- [(2S)-1-methylpyrrolidin-2-yl] pyridine  
Structure:



Physical form: Colourless or brownish viscous liquid which is volatile and hygroscopic.

Solubility: Soluble in water and miscible with ethanol.

Molecular formula: C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>  
Molecular weight: 162.2

The source of nicotine used in the product complies with its European Pharmacopoeia monograph.

The manufacturer of the drug substance holds a valid EDQM (European Directorate for the Quality of Medicines and Healthcare) Certificate of Suitability. The quality of the substance is suitably controlled in line with the current edition of the relevant European Pharmacopoeia Monograph.

The manufacturing process, control of materials, control of critical steps, validation and process development for nicotine were assessed and approved by the EDQM in relation to the granting of the Certificate of Suitability and are therefore satisfactory.

An appropriate specification with suitable test methods and limits is provided for the drug substance. The methods of testing and limits for related substances and residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all reference standards used.

The container-closure system and the re-test period comply with that which is specified on the Certificate of Suitability.

### DRUG PRODUCT

#### Other ingredients

Other ingredients consist of pharmaceutical excipients propylene glycol, anhydrous ethanol, trometamol, poloxamer 407, glycerol, sodium hydrogen carbonate, levomenthol, mint flavour, cooling flavour, sucralose, acesulfame potassium, hydrochloric acid and purified water.

All of the ingredients with the exception of sucralose, mint flavour, and cooling flavour comply with their relevant European Pharmacopoeia monographs. Sucralose complies with

United States Pharmacopoeia – National Formulary (USP-NF) monograph requirements. Mint flavour and cooling flavour both comply with in-house specifications.

None of the excipients used contain material of animal or human origin.

### **Pharmaceutical Development**

The objective of the development programme was to provide a NRT product with a fast onset combined with a satisfactory consumer sensory acceptance.

The applicant has provided a suitable product development section. Valid justifications for the use and amounts of each excipient have been provided.

### **Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. In-process controls are satisfactory and are supported by validation data. Process validation data on pilot-scale batches have been provided and are satisfactory. A commitment to perform process validation on future commercial-scale batches has been provided.

### **Finished Product Specification**

The finished product specification is satisfactory. 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 have been provided for any working standards used.

### **Container-Closure System**

The product is packaged in a bottle composed of polyethylene terephthalate (PET) containing 13.2 ml of solution. One bottle contains at least 150 sprays. The bottle is placed in a dispenser with a mechanical spray pump. The product comes in pack sizes of 1 dispenser and 2 dispensers. Not all pack sizes may be marketed.

Specifications and certificates of analysis have been provided. All primary product packaging complies with EU legislation and the EU Directive regarding contact with food.

### **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 storage instructions ‘Do not store above 25°C’. This is satisfactory.

### **Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labelling**

The SmPC, PIL and labelling are pharmaceutically acceptable. The UK approved SmPC, PIL and label are included at the end of this report. The labelling is satisfactory and fulfils the statutory requirements for Braille.

No user testing results have been submitted for the PIL for this product. This is because the applicant has submitted a satisfactory bridging report cross-referring to the approved PIL for Nicorette Inhaler, currently authorised to McNeil Products Limited (PL 15513/0179). The PIL is satisfactory.

**MAA Form**

This is pharmaceutically satisfactory.

**Quality Overall Summary**

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Quality Conclusion**

From a quality point of view, it is recommended that a Marketing Authorisation is granted for this application.

## NON-CLINICAL ASSESSMENT

With the exception of the risk assessment studies of extractables and leachables, no new non-clinical data have been supplied with this application and none are required for an application of this type. All studies were performed in accordance with Good Laboratory Practice (GLP).

An oromucosal spray was chosen as the delivery system as nicotine is readily absorbed across the oral mucosa. The container closure system comprises of a spray pump crimped onto a PET plastic vial, with an actuator press fitted to the pump. Both actuator and pump produce together a fine mist of spray for oromucosal use. All primary packaging materials conform to food grade regulations and comply with the European directives 2002/72/EC and/or 2002/79/EC where applicable.

### **Risk Assessment of Extractables and Leachables**

To provide additional reassurance in terms of patient safety, the applicant has performed a toxicological risk assessment of extractables and leachables from the components of the drug delivery device. These studies provide qualitative compositional information which allow for an assessment of the potential toxicological risks associated with the use of the polymeric materials in the final application. They also provide the information required to develop a protocol for target analysis of potential leachables in the final product formulation.

The toxicological risk assessment of extractables and leachables from the components of the drug delivery device showed that none of the materials in the drug-delivery device posed a risk from extractable/leachable substances within their products.

### **Environmental Risk Assessment**

An Environmental Risk Assessment (ERA) has been provided. Results are shown below:

<b>Substance (INN/Invented Name): Nicotine</b>			
<b>PBT screening</b>	<b>Result</b>		<b>Conclusion</b>
Bioaccumulation potential- log $K_{ow}$	1.17 (<4.5 threshold)		Potential PBT (N)
<b>PBT-statement :</b>	The compound is considered as PBT		
<b>Phase I</b>			
<b>Calculation</b>	<b>Value</b>	<b>Unit</b>	<b>Conclusion</b>
PEC <sub>surface water</sub> , default or refined (e.g. prevalence, literature)	0.38	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
<b>Phase II Physical-chemical properties and fate</b>			
<b>Study type</b>	<b>Results</b>		<b>Remarks</b>
Predicted No Effect Concentration (PNEC)	PNEC <sub>water</sub> = 290 µg/L PNEC <sub>ground water</sub> = 1.8 µg/L PNEC <sub>microorganism</sub> = 1000 µg/L		
PEC <sub>groundwater</sub>	0.10 µg/L		
Calculation of PEC:PNEC ratios	PEC <sub>surfacewater</sub> :PNEC <sub>water</sub> = 0.0013 PEC <sub>groundwater</sub> :PNEC <sub>groundwater</sub> = 0.033 PEC <sub>surfacewater</sub> :PNEC <sub>microorganism</sub> = 0.00038		< 1 threshold < 1 threshold < 0.1 threshold



Considering the above data, nicotine is not expected to pose a risk to the environment. Oromucosal Nicotine Spray 1 mg/spray is not expected to significantly alter the concentration of nicotine, its metabolites or degradation products in the environment and therefore, is unlikely to pose a risk to the environment.

**Non-Clinical Overview**

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

**Non-Clinical Conclusion**

From a non-clinical perspective, it is recommended that a Marketing Authorisation is granted for this application.

## CLINICAL ASSESSMENT

### Clinical Pharmacology

To support the application, four pharmacokinetic studies and one low-intervention use study have been provided.

#### 1) A single-dose pharmacokinetic study comparing different regimens of 1mg Oromucosal Nicotine Spray (ONS) in healthy smokers.

The primary objectives were:

- 1) to investigate the relationship between the dose of nicotine given with ONS (1, 2, 3, and 4 mg as single doses), and conventional pharmacokinetic parameters indicating the speed and extent of nicotine uptake.
- 2) to test, with the 2 mg and 4 mg doses, the effect of a 20-second delay in the sequence of sprays on these pharmacokinetic parameters. The overall test included a test of an interaction between dose and delay.

Secondary objectives included assessing safety of each treatment regimen.

Subjects received single doses of nicotine on six different treatment visits. Blood samples were collected pre- and up to 8 hours post dose. A washout period of at least 36 hours separated the treatment visits.

The pharmacokinetic parameters for each treatment regimen are presented below.

Treatment	AUC <sub>10min</sub> * (ng/mLxh)	C <sub>max</sub> (ng/mL)	t <sub>max</sub> ** (min)	AUC <sub>t</sub> (ng/mLxh)	AUC <sub>∞</sub> (ng/mLxh)	t <sub>1/2</sub> (h)
1 mg	0.56±0.28	4.1±2.2	8	8.2±3.5	10.3±3.8	3.0±0.96
2 mg	0.84±0.49	7.3±3.2	10	15.9±5.9	18.8±6.7	2.7±1.1
3 mg	1.26±0.67	10.7±4.4	9	24.8±8.7	28.7±10.3	2.6±0.56
4 mg	1.50±0.68	13.7±3.9	9	33.0±12.6	37.1±15.2	2.4±0.44
2 mg delay	0.78±0.40	6.6±2.2	10	16.7±6.5	20.0±8.2	2.7±0.63
4 mg delay	1.33±0.69	12.7±5.0	10	31.0±11.8	35.2±14.8	2.7±0.94

\* Not corrected for baseline, \*\* Median

The ratios between doses in pharmacokinetic parameters are presented below.

Comparison	C <sub>max</sub>	AUC <sub>t</sub>	AUC <sub>∞</sub>	AUC <sub>10min</sub>
2 mg vs. 1 mg	179% (153-210)	195% (175-218)	181% (163-200)	141% (117-171)
3 mg vs. 2 mg	145% (123-171)	154% (138-173)	149% (134-165)	148% (122-179)

Comparison	C <sub>max</sub>	AUC <sub>t</sub>	AUC <sub>∞</sub>	AUC <sub>10min</sub>
4 mg vs. 3 mg	135% (114-161)	129% (115-146)	126% (113-141)	126% (103-155)

The estimate of  $\beta$ -coefficients (based on a mean regression coefficient) is presented below.

Parameter	Mean Regression Coefficient (95% C.I.)	Dose-linearity p-value
$C_{max}$	0.896 (0.784-1.008)	0.069
$AUC_{10min}$	0.699 (0.564-0.835)	<0.001
$AUC_t$	0.989 (0.910-1.067)	0.777
$AUC_{\infty}$	0.887 (0.814-0.959)	0.003

The ratios between pharmacokinetic parameters of treatment with and without delay between sprays are presented below.

Comparison	$C_{max}$	$AUC_t$	$AUC_{\infty}$	$AUC_{10min}$
Delay vs. No Delay 2 mg	95% (83-108)	104% (95-114)	104% (95-114)	93% (79-110)
Delay vs. No Delay 4 mg	94% (81-109)	100% (90-110)	101% (91-111)	89% (73-108)

The results show that  $C_{max}$ ,  $AUC_{10min}$ ,  $AUC_t$  and  $AUC_{\infty}$  of the ONS increase between 1 mg and 4 mg dosing regimen in a linear manner. A 20-second delay between sprays with the 2 mg and 4 mg ONS dose does not affect  $C_{max}$ ,  $AUC_t$  and  $AUC_{\infty}$  to an important extent.

## 2) A multiple-dose, open, randomised, low-intervention, pilot study on usage patterns of 1mg Oromucosal Nicotine Spray (ONS) given as either fixed or flexible doses.

The primary objective was to investigate and evaluate usage patterns of Oromucosal Nicotine Spray (ONS) during a 3-week period, when subjects were given either fixed or flexible directions for use of the treatment for smoking cessation.

Secondary objectives included assessing safety of each treatment regimen.

Results showed there were no significant differences in relief of craving or relief of withdrawal symptoms between the fixed-dosage and flexible-dosage regimens. The use of ONS was in generally lower than the recommended dosage in both the fixed- and flexible-dosage groups. Initially the usage of ONS was higher for the fixed- than the flexible-dosage. However, this difference disappeared over the 3-week period. The number of subjects using the spray above the maximum recommended level was very few.

## 3) A single-dose study to compare the pharmacokinetics of Oromucosal Nicotine Spray (ONS) versus NiQuitin 4mg Lozenges and Nicorette 4mg Gum.

The primary objective of this study was to compare the single-dose pharmacokinetics of one spray, two consecutive sprays and four consecutive sprays of Oromucosal Nicotine Spray (ONS) 1 mg, with those of NiQuitin Lozenge 4 mg, and Nicorette Gum 4 mg. Blood samples were taken pre- and up to 12 hours post dose.

Secondary objectives included assessing safety of each treatment regimen.

The pharmacokinetic parameters for each treatment regimen are presented below.

	<b>ONS 1 mg</b>	<b>ONS 2 mg</b>	<b>ONS 4 mg</b>	<b>Nicotine lozenge 4 mg</b>	<b>Nicorette gum 4 mg</b>
N	40	40	39	42	41
T <sub>max</sub> <sup>*</sup> (min)	10	12.5	10	45	30
cC <sub>max</sub> (ng/mL)	3.3 ± 1.5	5.3 ± 2.1	9.1 ± 3.0	7.0 ± 2.1	7.8 ± 2.7
AUC <sub>10min</sub> <sup>**</sup> (h*ng/mL)	0.48 ± 0.23	0.64 ± 0.33	0.96 ± 0.42	0.33 ± 0.20	0.33 ± 0.19
cAUC <sub>t</sub> (h*ng/mL)	6.6 ± 3.7	12.2 ± 4.0	23.7 ± 9.0	24.3 ± 11.1	21.1 ± 8.0
cAUC <sub>∞</sub> (h*ng/mL)	8.2 ± 4.1	14.0 ± 4.2	25.9 ± 9.4	26.7 ± 11.9	23.0 ± 8.4
T1/2 (h)	2.89 ± 1.19	2.63 ± 0.92	2.56 ± 0.72	2.87 ± 0.75	2.45 ± 0.75

\* Median, \*\* Not corrected for baseline

The ratios of pharmacokinetic parameters for each ONS treatment regimen versus NiQuitin Lozenge 4 mg are presented below.

<b>Parameter</b>	<b>Comparison vs. Nicotine lozenge 4 mg</b>		
	<b>ONS 1 mg</b>	<b>ONS 2 mg</b>	<b>ONS 4 mg</b>
cC <sub>max</sub> (ng/mL)	46.8% (41.7-52.5%)	76.9% (68.5-86.3%)	134% (119-151%)
AUC <sub>10min</sub> (h*ng/mL)	158% (136-183%)	215% (185-250%)	341% (293-398%)
cAUC <sub>t</sub> (h*ng/mL)	27.5% (25.1-30.2%)	55.6% (50.6-61.0%)	108% (98.1-119%)
cAUC <sub>∞</sub> (h*ng/mL)	32.0% (29.4-34.8%)	58.0% (53.2-63.2%)	107% (97.7-116%)

The ratios of pharmacokinetic parameters for each ONS treatment regimen versus Nicorette Gum 4 mg are presented below.

<b>Parameter</b>	<b>Comparison vs. Nicorette gum 4 mg</b>		
	<b>ONS 1 mg</b>	<b>ONS 2 mg</b>	<b>ONS 4 mg</b>
cC <sub>max</sub> (ng/mL)	41.7% (37.2-46.8%)	68.6% (61.1-77.0%)	120% (107-135%)
AUC <sub>10min</sub> (h*ng/mL)	148% (128-173%)	203% (174-236%)	322% (276-374%)
cAUC <sub>t</sub> (h*ng/mL)	29.3% (26.7-32.2%)	59.3% (54.0-65.1%)	115% (105-126%)
cAUC <sub>∞</sub> (h*ng/mL)	34.4% (31.5-37.5%)	62.3% (57.2-67.9%)	115% (105-125%)

The ratios of pharmacokinetic parameters between the ONS treatments are presented below.

<b>Parameter</b>	<b>ONS 4 mg vs. 2 mg</b>	<b>ONS 4 mg vs. 1 mg</b>	<b>ONS 2 mg vs. 1 mg</b>
cC <sub>max</sub> (ng/mL)	175% (155-196%)	287% (255-323%)	164% (146-185%)
AUC <sub>10min</sub> (h*ng/mL)	159% (136-185%)	217% (186-253%)	137% (117-159%)
cAUC <sub>t</sub> (h*ng/mL)	194% (177-213%)	392% (357-432%)	202% (184-222%)
cAUC <sub>∞</sub> (h*ng/mL)	184% (169-200%)	333% (305-364%)	181% (166-198%)

The results show that C<sub>max</sub>, AUC<sub>inf</sub> and AUC<sub>t</sub> for the ONS 4mg are slightly higher than for Nicorette Gum 4 mg. Also, C<sub>max</sub> for the ONS 4mg is higher than for NiQuitin Lozenge 4 mg (AUC<sub>t</sub> and AUC<sub>inf</sub> are comparable). AUC<sub>10mins</sub> is higher for the ONSs formulation (1mg, 2mg and 4mg) compared to both Nicorette Gum 4 mg and NiQuitin Lozenge 4 mg formulations.

The 1mg and 2mg ONS treatments show a lower  $C_{max}$ ,  $AUC_t$  and  $AUC_{inf}$  compared to both Nicorette Gum 4 mg and NiQuitin Lozenge 4 mg formulations.  $C_{max}$ ,  $AUC_t$  and  $AUC_{inf}$  seem to increase with the dose, as shown in the interval between 1mg and 4mg.

#### 4) A multiple-dose study to compare the steady state pharmacokinetics of Oromucosal Nicotine Spray (ONS) versus NiQuitin 4mg Lozenges and Nicorette 4mg Gum.

The primary objective of this study was to compare the steady state nicotine pharmacokinetics ( $C_{max}$ ,  $C_{av}$  and  $AUC_t$ ) of Oromucosal Nicotine Spray (ONS) 2 mg administered every 30 minutes and 2 mg every hour, respectively, versus that of NiQuitin Lozenge 4 mg every hour and Nicorette Gum 4 mg every hour.

Secondary objectives included assessing safety of each treatment regimen.

Blood samples were collected pre- and up to 12 hours post dose.

The steady state pharmacokinetic parameters are presented below.

	ONS 2 mg/h	ONS 2 mg/30 min	NiQuitin™ lozenge 4 mg/h	NICORETTE® gum 4 mg/h
$T_{max}^*$ (min)	10	10	25	30
$C_{max}$ (ng/mL)	17.1 ± 5.0	31.4 ± 9.8	29.0 ± 11.0	27.3 ± 8.6
$C_{min}$ (ng/mL)	11.7 ± 4.0	25.3 ± 8.4	22.1 ± 9.7	19.0 ± 7.0
$C_{av}$ (ng/mL)	14.6 ± 4.5	28.8 ± 9.2	25.5 ± 9.9	23.3 ± 7.5
$AUC_t$ (ng/mL.xh)	14.6 ± 4.5	14.4 ± 4.6	25.5 ± 9.9	23.3 ± 7.5
PTF (%)	38.4 ± 14.9	21.7 ± 8.7	29.1 ± 10.7	36.3 ± 12.8
Swing (%)	50.3 ± 23.5	25.2 ± 11.6	35.1 ± 15.6	46.4 ± 20.4

\* median

The ratios of pharmacokinetic parameters between treatments are presented below.

	ONS 2 mg/h		ONS 2 mg/30 min	
	vs. NiQuitin™ lozenge	vs. NICORETTE® gum	vs. NiQuitin™ lozenge	vs. NICORETTE® gum
$C_{max}$ (ng/mL)	61.1% (55.9-66.7)	63.6% (58.1-69.6)	109.5% (100.1-119.9)	114.1% (104.0-125.1)
$C_{av}$ (ng/mL)	59.5% (54.6-64.7)	63.5% (58.3-69.3)	114.6% (105.1-124.9)	122.4% (112.0-133.7)
$AUC_t$ (ng/mL.xh)	59.5% (54.6-64.7)	63.5% (58.3-69.3)	57.3% (52.5-62.4)	61.2% (56.0-66.9)
$T_{max}^{**}$ (min)	-10 (-15- -5)	-15 (-20- -10)	-10 (-20- -8)	-15 (-20- -9)
$C_{min}$ (ng/mL)	57.1% (49.9-64.4)	65.1% (58.3-72.0)	123.4% (107.4-139.5)	139.0% (125.2-152.8)
PTF (%)	147.2% (115.9- 178.6)	118.1% (93.3-142.9)	81.5% (65.8-97.1)	65.5% (48.5-82.4)
Swing (%)	166.2% (124.8- 207.5)	125.8% (94.9-156.7)	81.1% (63.7-98.5)	62.8% (43.9-81.7)

\* Estimated ratios based on models for log-transformed values for  $C_{max}$ ,  $C_{av}$  and  $AUC_t$ ; estimated ratios based on subjects' untransformed individual ratios for  $C_{min}$ , PTF and swing and estimated median difference for  $t_{max}$ .

\*\* Median

The pharmacokinetic parameters for self- versus staff-administered ONS treatments are presented below.

	ONS 2 mg/h self- administration	ONS 2 mg/h staff- administration	Ratio self- vs. staff- administration*
$C_{1h}$ (ng/mL)	4.7 ± 1.6	5.0 ± 1.5	91.8% (84.7-99.5)
$C_{max}$ (ng/mL)	16.5 ± 6.1	17.1 ± 5.0	92.3% (85.6-99.5)
$C_{av}$ (ng/mL)= $AUC_t$ (ng/mLxh)	14.3 ± 5.6	14.6 ± 4.5	93.8% (86.9-101.3)

	ONS 2 mg/h self- administration	ONS 2 mg/h staff- administration	Ratio self- vs. staff- administration*
$T_{max}^{**}$ (min)	15	10	5 (0-10)
$C_{min}$ (ng/mL)	11.5 ± 4.7	11.7 ± 4.0	98.0% (88.9-107.0)
PTF (%)	35.6 ± 14.2	38.4 ± 14.9	104.5% (84.9-124.2)
Swing (%)	46.1 ± 24.8	50.3 ± 23.5	109.8% (84.0-135.6)

\* Estimated ratios based on models for log-transformed values for  $C_{1h}$ ,  $C_{max}$  and  $AUC_t$ , estimated ratios based on subjects' untransformed individual ratios for  $C_{min}$ , PTF and swing and estimated median difference for  $t_{max}$ .

\*\* Median

The results show  $C_{max}$ ,  $C_{av}$  and  $AUC_t$  of the ONS 2 mg every hour are lower than those for NiQuitin Lozenge 4 mg every hour and Nicorette Gum 4 mg every hour. They also suggest that  $C_{max}$  and  $C_{av}$  of the ONS 2 mg every 30 minutes are higher than those for NiQuitin Lozenge 4 mg every hour and Nicorette gum 4 mg every hour. The bioavailability of nicotine from ONS is slightly higher than from NiQuitin Lozenge 4 mg and Nicorette Gum 4 mg.

##### 5) An open-label, four-way crossover, single-dose study, comparing the early pharmacokinetics of Oromucosal Nicotine Spray (ONS) 2mg versus Nicorette Gum 2mg in healthy smokers.

The primary objective was to compare the early pharmacokinetics of nicotine after either spraying a single dose of ONS 2 mg straight into the mouth or chewing a Nicorette® gum 2 mg for 30 minutes. Ratios between nicotine  $AUC_{10min}$  and  $C_{max}$  for the two treatments were determined as primary measures of differences between the products.

Each treatment visit consisted of a single morning dose of nicotine, an 8-hour nicotine-free interval and a second single nicotine dose from the same type of product as given in the morning. A washout period of at least 36 hours separated the treatment visits. Blood samples were taken pre- and up to 8 hours post dose.

The results showed a higher absorption for the ONS formulations compared with the gum.

No clinical Phase III study addressing clinical efficacy have been provided, however, the MAH have supplied the following data comparing the pharmacokinetic parameters of Nicorette QuickMist Mouthspray with that of Nicorette gum (2mg, 4mg), Nicorette nasal spray NNS (1mg) and smoking a cigarette in the table below:

The pharmacokinetic parameters of Nicorette QuickMist mouth spray in comparison with Nicorette gum (2mg, 4mg), NNS and smoking a cigarette.

	<b>Maximum plasma nicotine levels</b>	<b>Time to reach maximum plasma nicotine levels</b>
Cigarette 1 puff/min over 10 minutes	18.6 ng/ml	11.2 minutes
<b>NNS 1mg</b>		
Johansson	8.1ng/mL	11.5 minutes
Lunell *	6.03ng/mL	15 minutes
Gourlay	5.4ng/mL	17.5 minutes
<b>Nicorette QuickMist (2mg dose)</b>		
Study 5	7.0ng/mL	8-16 minutes
Study 3	5.3ng/mL	8-16 minutes
<b>Nicorette gum 2mg</b>		
Study report 5	5.4ng/mL	30minutes
<b>Nicorette gum 4mg</b>		
Study 3	7.8ng/mL	30 minutes

\* peak not covered by the study.

The applicant concludes that the

- rate of venous absorption from Nicorette QuickMist is similar to that from the currently authorised as GSL nasal spray (NNS) but slower than from a cigarette
- rate of arterial absorption of Nicorette QuickMist is considerably slower than that from a cigarette
- extent of absorption from Nicorette QuickMist (single administration of recommended dose, 2 sprays – 2mg) is somewhat higher than for 2mg Nicorette gum but lower than for the 4mg gum or 4mg lozenge.

### **Overall Conclusions on Clinical Pharmacology**

The applicant is not claiming bioequivalence with other NRT formulations. In fact, Nicorette QuickMist is not bioequivalent with the other NRT formulations, but plasma levels are similar to those achieved with other forms of NRT in both single-dose and steady state.

It has been shown that the absorption of nicotine from ONS formulations is fast. The plasma level over the first 10 minutes after administration was significantly higher for ONS than for the gum and lozenge formulations. The maximum concentration with the highest recommended single-dose of ONS was lower than with nicotine lozenge 4mg and nicorette gum 4mg. AUC<sub>t</sub> with the 4mg dose was comparable with nicotine lozenge and gum 4 mg.

The multiple-dose pivotal study showed that the exposure of nicotine at equal strengths is slightly higher for the ONS than for the lozenge and gum formulations. The results of this study showed that the ONS provides a slightly higher bioavailability of nicotine than the lozenge and gum formulations.

The difference of pharmacokinetic profiles (ONS vs reference products) is expected to be of little clinical significance for a product that is self-titrated to a subject's needs by frequency of dosing.

The higher  $C_{max}$  of the oromucosal spray 4mg when compared with the 4mg chewing gum and 4mg lozenge has been justified by the applicant by comparison to levels of nicotine obtained after administration of a nasal spray and smoking itself and is considered acceptable.

The local tolerability and in particular the oromucosal irritation is worse for the oromucosal spray than for the gum, although this levelled-off after 10 minutes.

### **Efficacy**

No new data has been provided.

### **Safety**

The overall safety profile of nicotine products is well-known as a large number of nicotine replacement products are available. The number and type of adverse events are comparable with ONS versus other forms of NRT.

There is increased number of “hiccups” episodes for the ONS compared with the other formulations (there are two cases of withdrawal due to hiccups). One of the “Very common” adverse events was “burning lips” (or burning sensation). This adverse event is not frequently reported for the other NRTs and it appears to be specific for ONS formulations. This event was described as mild and did not require any treatment. In general, there is an increased frequency of local irritation of the mouth, although none of these were severe.

The product is generally well-tolerated.

### **Clinical Expert Reports**

The clinical overview and clinical summary have been written by a suitably qualified person and are satisfactory.

### **Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling**

The SmPCs, PIL and labelling are clinically satisfactory.

### **MAA Forms**

The MAA forms are clinically satisfactory.

### **Discussion**

The clinical efficacy, safety and pharmacology of the active ingredient nicotine are already well-established and documented. The application contains an adequate review of clinical data. From a clinical point of view the risk-benefit is considered positive.

### **Clinical Conclusion**

From a clinical perspective, it is recommended that a Marketing Authorisation is granted for this application.



## OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

### QUALITY

The important quality characteristics of Nicorette QuickMist 1 mg/spray mouthspray 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

With the exception of the risk assessment studies of extractables and leachables, no new non-clinical data have been supplied with this application and none are required for an application of this type.

The toxicological risk assessment of extractables and leachables from the components of the drug delivery device showed that none of the materials in the drug-delivery device posed a risk from extract/leachable substances within their products.

A satisfactory ERA was provided. Nicotine is not expected to pose a risk to the environment.

### CLINICAL

Single-dose and steady state pharmacokinetic studies have shown that plasma levels of nicotine are the same between the proposed product and other similar products on the market (such as NiQuitin Lozenge 4 mg and Nicorette Gum 4 mg).

No new or unexpected safety concerns arise from this application. The adverse event profile of this product is broadly similar with those for other nicotine-replacement therapies.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

### RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The application contains an adequate review of clinical data. Clinical experience with nicotine is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

**NICORETTE QUICKMIST 1MG/SPRAY MOUTHSPRAY  
PL 15513/0357**

**STEPS TAKEN FOR ASSESMENT**

1	The MHRA received the Marketing Authorisation application on 15 <sup>th</sup> December 2009.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 30 <sup>th</sup> December 2009.
3	Following assessment of the application, the MHRA requested further information on the quality sections of the dossier on 9 <sup>th</sup> March 2010 and 9 <sup>th</sup> September 2010.
4	The applicant responded to the MHRA's requests, providing further information on the quality sections of the dossier on 12 <sup>th</sup> May 2010, 28 <sup>th</sup> October 2010 and 25 <sup>th</sup> November 2010.
5	The application was determined on 30 <sup>th</sup> November 2010.

**NICORETTE QUICKMIST 1MG/SPRAY MOUTHSPRAY  
PL 15513/0357**

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>

## Annex I

**APPLICATION FOR CLASSIFICATION OF NICORETTE QUICKMIST AS GSL**

<b>MA no.</b>	PL 15513/0357
<b>Product name</b>	Nicorette QuickMist Mouthspray

**INTRODUCTION****Background**

This application seeks to obtain a Marketing Authorisation for Nicorette QuickMist Mouthspray and also classify it as a GSL product for the relief of nicotine craving and withdrawal symptoms as an aid to smoking cessation in adults and children aged 12 and over. 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 recently a “harm reduction” indication has been granted for Nicorette inhalator (11<sup>th</sup> December 2009) with the advice from Commission of Human Medicines (CHM), endorsed by the Licensing Authority, that this should be the indication for all other NRT products licensed at the time. However, new formulations, such as Nicorette QuickMist Mouthspray, would need to be assessed on a case-by-case basis.

Currently all the different formulations of medicinal nicotine containing products (including Nicorette nasal spray - NNS) have GSL status but most were originally either Prescription Only Medicines (POM) or Pharmacy medicines (P). Nevertheless, different strengths (such as the 25mg patch – Nicorette 25mg Invisi patch) and formats (such as the Nicorette Combi PL 15513/0359 - Nicorette Invisi patch (15mg) plus Nicorette icy white gum (2mg)) were granted GSL status at the time of authorisation.

**Proposed dose schedule**

For QuickMist each 0.07ml contains 1mg of nicotine which corresponds to 1mg nicotine/spray dose. The SmPC advises:

- Do not use more than 2 sprays at one time
- Up to 4 sprays per hour
- Maximum 64 sprays (4 sprays per hour over 16 hours) per 24 hour period.

**Proposed “enhanced” post-marketing surveillance**

It has been agreed between the MHRA and the applicant that the following measures (relating mainly to potential abuse/misuse) will be implemented if Nicorette QuickMist Mouthspray is authorised with GSL status.

- regular monthly meeting when the applicant will monitor for signals suggesting inappropriate use (abuse/misuse)
- annual PSURs for the 1<sup>st</sup> 3 years
- specific section in each Periodic Safety Update Report (PSUR) relating to abuse/misuse
- routinely monitored sales data.

Similar measures were implemented following the NNS P to GSL switch after CHM raised concerns about potential abuse/misuse. The MAH propose to submit the findings of this “enhanced pharmacovigilance” in the PSUR they will submit on 30<sup>th</sup> October 2010.

**CRITERION FOR GSL STATUS**

Section 51 of the Medicines Act 1968 states that “GSL may be appropriate for medicines which can, with reasonable safety be sold or supplied otherwise than by or under the supervision of a pharmacist”. “Reasonable safety” may be usefully defined as “Where the hazard to health and the risk of misuse and the need for special precautions in handling are small, and where wider sale would be a convenience to the purchaser”.

**PHARMACEUTICAL ASSESSMENT**

The applicant has evaluated the droplet size of the spray, demonstrating that the mean droplet size was approximately 80µm at 3cm distance and 70µm at 6cm distance. The percentage of droplets smaller than 10µm, thus potentially available for inhalation, was below 1.5%. The risk of droplet deposition in the lung is considered to be negligible; therefore droplet size is considered acceptable.

Additionally, the SmPC and leaflet include advice not to inhale whilst using the spray. This is consistent with advice on other GSL spray products and is acceptable.

**Rationale for application**

The MAH states that the pharmacological and pharmacokinetic properties of Nicorette QuickMist Mouthspray most closely resemble that of Nicorette nasal spray (NNS), whilst neither matches the speed of absorption of nicotine from smoking a cigarette. From 4 placebo-controlled studies identified, the Cochrane collaboration (Stead et al 2008) concluded that the relative risk (RR) of abstinence at 6 months was 2.02 (95% CI:1.49 to 2.73) for NNS which was higher than any other currently available forms of NRT, although it should be noted that the confidence intervals (CIs) were wide.

Taking this into account, the MAH’s rationale for the classification of Nicorette QuickMist Mouthspray as GSL is that

- all forms of NRT increase the likelihood of a smoker quitting
- the use of NNS doubles the chances of smoking cessation compared to placebo (with Nicorette QuickMist Mouthspray producing comparable plasma nicotine levels to NNS)
- in order to encourage quitting, it is appropriate to offer smokers the widest choice of NRT products and make these as widely available as possible.

**CLINICAL ASSESSMENT**

The data have already been evaluated in the clinical assessment report of the national abridged application for Nicorette QuickMist Mouthspray made under Article 8.3 of Directive 2001/83/EC (amended by 2004/27/EC) a line extension application, which proposes a new pharmaceutical form but with GSL status. In summary this concludes that

- the clinical efficacy, safety and pharmacology of the active ingredient nicotine are already well-established and documented.
- the 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.

**Pharmacokinetic (PK) profile/Efficacy**

- No clinical Phase III study addressing clinical efficacy have been provided, however, the MAH have supplied data comparing the pharmacokinetic parameters of Nicorette QuickMist Mouthspray with that of Nicorette gum (2mg, 4mg) and NNS (1mg),

which is summarised in the clinical assessment section of this PAR. The results show that the plasma levels of the nicotine in Nicorette QuickMist are similar to other forms of NRT.

### Safety

As noted above no clinical efficacy study but events from the 4 pharmacokinetic studies and one phase 2 pilot intervention study the reactions were collected. The only treatment related reaction that appears to be specifically related to Nicorette QuickMist is a burning sensation of the lips. The MAH have submitted “representative” data from study 2 (refer to the clinical assessment section in this PAR) where 38 of 256 subjects (14.8%) experienced burning of the lips, of these 3 (1.2%) were described as severe. The conclusions drawn were that this was “not considered a major problem, due to its transient nature and likely relationship to poor spray technique which should improve with time”. Otherwise the pattern, frequency and type of adverse events is considered by the MAH to be typical of NRT products and as expected for an oral NRT product, during the first few days of use, mouth and throat irritation may occur. As with NNS, these and other commonly reported events (such as headache, hiccups, nausea, excess salivation, dizziness, dyspepsia and watering eyes) were dose-related but diminished with time.

### Hazard to health

#### *Comparison with continuing to smoke*

Smoking is a well-known hazard to health but nicotine is only one element of tobacco smoke. The position taken by CSM relating to NRT is that there are no circumstances in which it is safer to smoke than to use NRT.

#### *Direct risk of adverse effects*

All other currently available forms of NRT has been considered suitable for use as GSL and Nicorette QuickMist has comparable nicotine levels to those achieved by NNS and nicotine containing gums (ie products with GSL status). In addition, as noted above, apart from the local effect (burning sensation of lips), the Adverse Drug Reactions (ADRs) reported with Nicorette QuickMist gives no indication of a differing profile from other GSL available forms.

#### *Appropriate use*

Most smokers are adept at titrating their nicotine levels to their own “comfort zone”. A 3-week, multiple dose study 2 of fixed and flexible dosing showed that study subjects were able to use the spray and use it as directed (regardless of which regimen to which they were allocated).

#### *Indirect risk*

It is not expected that Nicorette QuickMist would mask other disease or delay diagnosis of any condition.

### Conclusion

Both levels of nicotine achieved by use of Nicorette QuickMist and the expected safety profile give no indication that this product would pose any more of a hazard to health than other NRT products currently available on the GSL.

### Risk of misuse

Transferred dependence from smoking to NRT does occur but it is not very common, is considerably less harmful than continuing to smoke and is an easier habit to break.

The pharmacokinetic profile of a drug has been considered a contributing factor in the development of dependence (and/or abuse). Elements of a drug's profile that predict greater risk include – rapid onset, high blood concentrations, high frequency of use and few adverse events. Rapid onset is associated with drug-seeking for subjective effects and as noted above, following the use of Nicorette QuickMist the arterial plasma nicotine concentrations were considerably lower than those reached whilst smoking a cigarette and were comparable with other GSL NRT forms. In a 3-week pilot study of 258 subjects (Study 2) the MAH state that no incidences of euphoria, light-headedness or other “typical abuse-related events” were reported.

### **Conclusion**

There are no particular characteristic of Nicorette QuickMist that make the risk of misuse more likely than for other GSL NRT products. In addition, the MAH propose to implement appropriate monitoring.

#### **Need for special precautions in handling**

The proposed SmPC – Section 4.4 includes the following advice and recommendations:

*‘Dangers in small children: Doses of nicotine tolerated by adults 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’.*

The PIL has a sub-section *Storing and disposal* which includes the following:

*‘Keep Nicorette QuickMist out of reach and sight of children and animals. Nicotine in high doses can be very dangerous and sometimes fatal if taken by small children’.*

*‘Disposed of Nicorette QuickMist sensibly and 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’.*

### **Conclusion**

The proposed product information contains clear directions on the responsible handling and disposal of the products in order to prevent accidental exposure to nicotine. There are no other issues in respect of special handling requirements.

#### **Sale would be a convenience to the purchaser**

Overall, there is not much difference in how well the various types of NRT work, so the choice mainly depends on personal preference. All other nicotine-containing products are on the GSL and, apart from the burning sensation of the lips, there appears to be no specific safety issues specific to Nicorette QuickMist.

### **Conclusion**

Any form of NRT may help a smoker attempting to quit, but personal preference can be important in meeting the specific needs of an individual. Therefore the more forms available the greater the likelihood of successful reducing/quitting smoking and having all currently available NRT products as GSL would be a convenience to those attempting to quit/reduce.

#### **Supply without supervision of a pharmacist**

Currently all other nicotine-containing products are available without the intervention of a pharmacist, and overall the data reviewed does not indicate why this should differ for Nicorette QuickMist.

**Conclusion**

Because of the similar PK and safety profile to other GSL NRT products, there is no reason to consider that Nicorette QuickMist could not be supplied and used without the supervision of a pharmacist.

**PRODUCT INFORMATION****SmPC – Annexe 4**

The SmPC is in line with the recommendations of the CSM Working Group on Nicotine Replacement Therapy (December 2005) and the CHM Working Group on Harm Reduction and NRT (2009).

**Patient Information Leaflet (PIL)**

The proposed PIL is satisfactory

**DISCUSSION**

Nicorette QuickMist is not bioequivalent to existing GSL products; however, plasma nicotine levels are comparable with other currently available GSL NRT products, particularly NNS. NNS has been reviewed by the Cochrane collaboration and is considered to have an adequate “efficacy” profile. Although specific safety data for Nicorette QuickMist is limited, there are no indications that the product cannot be used safely without the supervision of a pharmacist.

Under these circumstances, Nicorette QuickMist may be considered to be analogous to the nasal spray and therefore consultation on the apparent reclassification is not necessary.

**CONCLUSION**

Nicorette QuickMist should be classified as GSL, without the need to prior consultation.



## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Nicorette QuickMist 1mg/spray mouthspray

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

0.07 ml contains 1 mg nicotine, corresponding to 1 mg nicotine/spray dose.  
Excipient: ethanol (contains less than 100 mg of ethanol/spray dose).  
For a full list of excipients see section 6.1.

### 3 PHARMACEUTICAL FORM

Oromucosal spray.  
A clear to weakly opalescent, colourless to light yellow solution with a scent of peppermint.

### 4 CLINICAL PARTICULARS

#### 4.1 THERAPEUTIC INDICATIONS

Nicorette QuickMist 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 QuickMist is indicated in pregnant and lactating women making a quit attempt.

#### 4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The patient should make every effort to stop smoking completely during treatment with Nicorette QuickMist.

Behavioural therapy, advice and support will normally improve the success rate.

##### *Directions for use*

If you are using Nicorette QuickMist for the first time or if you have not used the spray for 2 days, you must first prime the spray pump.

##### *Priming*

1. Point the spray safely away from you and any other adults, children or pets that are near you.
2. Press the top of the QuickMist with your index finger 3 times until a fine spray appears.

Note: priming reduces the number of sprays you may get from Nicorette QuickMist.

After priming, point the spray nozzle as close to the open mouth as possible. Press the top of the dispenser and release one spray into your mouth, avoiding the lips. Do not inhale while spraying to avoid getting spray down your throat. For best results, do not swallow for a few seconds after spraying.

The patient should not eat or drink when administering the oromucosal spray.  
Care should be taken not to spray the eyes whilst administering the mouth spray.

##### *Adults and Children over 12 years of age*

Use 1 or 2 sprays when cigarettes normally would have been smoked or if cravings emerge. If after the first spray cravings are not controlled within a few minutes, a second spray should be used. If 2 sprays are required, future doses may be delivered as 2 consecutive sprays.

Most smokers will require 1-2 sprays every 30 minutes to 1 hour.

You may use up to 4 sprays per hour. Do not exceed 2 sprays per dosing episode and 64 sprays (4 sprays per hour over 16 hours) in any 24-hour period.

Each mouthspray contains at least 150 sprays.

Nicorette QuickMist 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 Nicorette QuickMist and as soon as they are able, reduce the number sprays used until they have stopped completely.

Smokers aiming to reduce cigarettes should use the Mouthspray, 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.

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 their Mouthspray are recommended to contact their pharmacist or doctor for advice.

#### 4.3 CONTRAINDICATIONS

Hypersensitivity to any component of the mouthspray.

Nicorette QuickMist is contraindicated in children and adolescents under 12 years.

#### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Any risks that may be associated with NRT are substantially outweighed by the well established dangers of continued smoking.

*Underlying cardiovascular disease:* In stable cardiovascular disease Nicorette QuickMist presents a lesser hazard than continuing to smoke. However dependent smokers currently hospitalised as a result of myocardial infarction, unstable or worsening angina including Prinzmetal's angina, 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 QuickMist 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.

*GI disease:* Swallowed nicotine may exacerbate symptoms in patients suffering from oesophagitis, gastritis or peptic ulcers and oral NRT preparations should be used with caution in these conditions.

*Renal or hepatic impairment:* Nicorette QuickMist should be used 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.

*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.

*Phaeochromocytoma and uncontrolled hyperthyroidism:* As nicotine causes release of catecholamines, Nicorette QuickMist should be used with caution in patients with uncontrolled hyperthyroidism or phaeochromocytoma.

*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.

*Excipients:* The mouthspray contains small amounts of ethanol (alcohol), less than 100 mg per spray.

#### 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No clinically relevant interactions between nicotine replacement therapy and other drugs has 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 fetus is lower than that expected with smoking tobacco. Stopping completely is by far the best option but if this is not achievable Nicorette QuickMist 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 fetus 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**

Nicorette QuickMist has no or negligible influence on the ability to drive and use machines.

#### **4.8 UNDESIRABLE EFFECTS**

Some symptoms may be related to nicotine withdrawal associated with stopping smoking. These can include 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, which is recognised as a clinically relevant symptom, is an important element in nicotine withdrawal after smoking cessation.

Nicorette QuickMist may cause adverse reactions similar to those associated with nicotine given by other means, including smoking, and these are mainly dose-dependent.

Most adverse events reported with Nicorette QuickMist occur during the early phase of treatment. During the first few days of treatment irritation to the mouth and throat may be experienced. Most patients will get used to this sensation after a few days.

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

Reported adverse events associated with Nicorette QuickMist include:

Body system	Incidence*	Reported adverse event
Psychiatric disorders <sup>1</sup>	Uncommon:	Anger <sup>1</sup> , anxiety <sup>1</sup> , insomnia <sup>1</sup> , restlessness <sup>1</sup>
Nervous system disorders:	Very common: Common:	Dysgeusia, headache Dizziness, paraesthesia
Eye disorders	Uncommon	Lacrimation increase, vision blurred
Cardiac disorders:	Common: Not known:	Palpitations Atrial fibrillation
Vascular disorders	Uncommon:	Flushing
Respiratory, thoracic and mediastinal disorders:	Very common: Common: Uncommon: Not known:	Hiccups Cough Rhinorrhoea Dyspnoea
Gastrointestinal disorders:	Very common: Common: Uncommon:	Nausea and vomiting symptoms, dyspepsia Aphthous stomatitis <sup>1</sup> , gingival bleeding <sup>1</sup> Abdominal pain, flatulence
Skin and subcutaneous tissue	Uncommon:	Dry skin, hyperhidrosis, rash,

disorders

Musculoskeletal, connective tissue and bone disorders	Uncommon:	Musculoskeletal pain
General disorders and administration site conditions	Very common:	Oral soft tissue pain and paraesthesia, stomatitis, salivary hypersecretion, burning lips, dry mouth
	Common:	Toothache, pharyngeal hypoaesthesia
	Uncommon:	Chest discomfort, dry throat, throat tightness, chest pain, fatigue <sup>1</sup> , irritability <sup>1</sup> , pain

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

<sup>1</sup> Symptoms known to be associated with cessation of tobacco smoking and nicotine withdrawal.

#### 4.9 OVERDOSE

*Symptoms:* The minimum lethal dose of nicotine in a non-tolerant man has been estimated to be 40 to 60mg. Symptoms of acute nicotine poisoning include nausea, vomiting, increased salivation, abdominal pain, diarrhoea, 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 general convulsions.

Doses of nicotine that are tolerated by adult smokers during treatment may produce severe symptoms of poisoning in small children and may prove fatal. Suspected nicotine poisoning in a child should be considered a medical emergency and treated immediately.

*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.

ATC code: N07B A01

Nicotine is an agonist at nicotine receptors in the peripheral and central nervous system and has pronounced CNS and cardiovascular effects.

Clinical studies have shown that nicotine replacement products can help smokers abstain from smoking by relieving these withdrawal symptoms. Compared to nicotine gum or nicotine lozenge, the absorption of nicotine from the mouth spray is more rapid (section 5.2) and based on prior experience with nicotine replacement therapy, this will result in a faster onset of relief of cravings and other 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

The pharmacokinetics of nicotine has been extensively studied, and variations in delivery format have been found to have significant effects on rate and extent of absorption.

The pharmacokinetics of the mouth spray has been studied in 4 studies. The studies included 141 subjects.

#### Absorption

The oral spray form means that the nicotine dose is administered instantaneously, and as a result the absorption of nicotine from the mouth spray is rapid: In trials, nicotine uptake from the oral nicotine spray was detected at 2 minutes, the first timepoint tested.

A maximum concentration of 7.0 ng/mL is reached within 16 minutes after administration of a 2 mg dose, as compared with a maximum concentration of 5.4 ng/mL at 30 minutes for nicotine gum 2 mg. Comparing the AUC over the first 10 minutes after administration the estimates of the mouth spray at a dose of 1 and 2 mg exceeds those of nicotine gum as well as nicotine lozenge at doses of 4 mg (0.48 and 0.64 h\*ng/mL vs. 0.33 and 0.33 h\*ng/mL).

AUC $\infty$  estimates show the bioavailability of nicotine administered by mouth spray is somewhat higher than that of nicotine gum or lozenge. The AUC $\infty$  of the mouth spray 2 mg measured 18.9 h\*ng/mL as compared with 16.2 h\*ng/mL for nicotine gum 2 mg. Allowing for differences in administered dose, bioavailability was also higher in a second study. The AUC $\infty$  of the mouth spray 2 mg measured 14.0 h\*ng/mL in comparison with 23.0 h\*ng/mL and 26.7 h\*ng/mL for and nicotine gum 4 mg and nicotine lozenge 4 mg, respectively.

Steady-state average nicotine plasma concentrations achieved after administration of the maximum dose (i.e. 2 sprays of the mouth spray 1 mg every 30 minutes) are in the order of magnitude approximately 28.8 ng/mL as compared with 23.3 ng/mL for nicotine gum 4 mg (1 gum, hourly) and 25.5 ng/mL for nicotine lozenge 4 mg (1 lozenge, hourly).

Given the rapid absorption and the similar, high relative bioavailability, the majority of the nicotine released from the mouth spray is apparently absorbed through the buccal mucosa.

### **Distribution**

Results of the pharmacokinetic studies of the mouth spray suggest that nicotine metabolism and elimination are independent of the choice of nicotine formulation, and thus results from studies with intravenous administration of nicotine are used to describe distribution, biotransformation, metabolism and excretion.

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 major nicotine-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.

### **Elimination**

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

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.

### **Linearity/non-linearity**

There is only a small deviation from dose-linearity of AUC $\infty$  and C<sub>max</sub> as shown when single doses of 1, 2, 3 and 4 sprays of the 1 mg mouth spray are given.

Characteristics in specific groups of subjects

#### *Renal Impairment*

Progressive severity of renal impairment is associated with decreased total clearance of nicotine.

Nicotine clearance was on average decreased by 50%, in subjects with severe renal impairment. Raised nicotine levels have been seen in smokers undergoing hemodialysis.

#### *Hepatic Impairment*

The pharmacokinetics of nicotine are unaffected in patients with mild liver impairment (Child-Pugh score 5) and decreased by 40-50% in patients 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, not justifying adjustment of dosage, has been demonstrated in healthy elderly patients.

**5.3 PRECLINICAL SAFETY DATA**

Nicotine was positive in some in vitro genotoxicity tests but there are also negative results with the same test systems. Nicotine was negative in in vivo tests.

Animal experiments have shown that nicotine exposure results in decreased birth-weight decreased litter size and decreased survival of offspring.

The results of carcinogenicity assays did not provide any clear evidence of a tumorigenic effect of nicotine.

**6 PHARMACEUTICAL PARTICULARS****6.1 LIST OF EXCIPIENTS**

Propylene glycol  
Anhydrous ethanol  
Trometamol  
Poloxamer 407  
Glycerol  
Sodium hydrogen carbonate  
Levomenthol  
Mint flavour  
Cooling flavour  
Sucralose  
Acesulfame potassium  
Hydrochloric acid  
Purified water

**6.2 INCOMPATIBILITIES**

Not applicable.

**6.3 SHELF LIFE**

2 years

**6.4 SPECIAL PRECAUTIONS FOR STORAGE**

Do not store above 25°C

**6.5 NATURE AND CONTENTS OF CONTAINER**

PET bottle containing 13.2 ml of solution. One bottle contains at least 150 sprays. The bottle is placed in a dispenser with a mechanical spray pump.

Pack Sizes: 1 dispenser, 2 dispensers

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 AUTHORISATION HOLDER**

McNeil Products Limited  
Foundation Park  
Roxborough Way  
Maidenhead  
Berkshire  
SL6 3UG  
UK

**8 MARKETING AUTHORISATION NUMBER(S)**

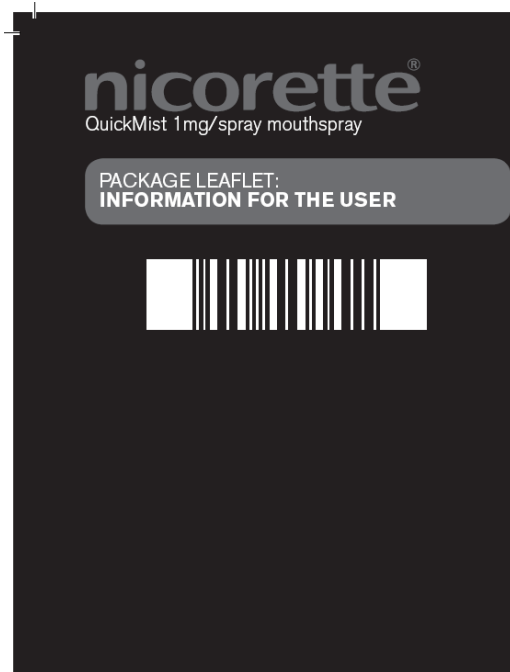
PL 15513/0357

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

30/11/2010

**10 DATE OF REVISION OF THE TEXT**

30/11/2010



nicorette®  
QuickMist 1mg/spray mouthspray  
nicotine

### What should you know about nicorette® QuickMist mouthspray

(nicotine 1 mg per spray)

Please read this leaflet carefully before you start using this medicine. It provides useful information on how to use it safely. Keep the leaflet, you might need it again.

If you think you are having side-effects, have any questions or are not sure about anything please ask your doctor, nurse or pharmacist.

## 1 What this medicine is for

Nicorette QuickMist 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 mouthspray to achieve this by using it to completely replace all your cigarettes.

However nicorette mouthspray 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 and 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. Details of Nicorette ActiveStop are at the end of this leaflet.



## What does Nicorette QuickMist do?

When you stop smoking 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 QuickMist, nicotine passes rapidly into your body through the lining of your mouth. This relieves the unpleasant 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.

For the best effect, ensure that you use nicorette QuickMist correctly – see "How to Use Nicorette QuickMist."

### Benefits you can get from using NRT instead of smoking

For the best effect, ensure that you use nicorette mouthspray correctly – see "How to Use Nicorette QuickMist."

**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 diseases 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 the 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.

## 2 Before using this medicine

### ⊗ Do not use Nicorette QuickMist:

- if you have an allergy to nicotine or any of the other ingredients.
- if you are 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, chest pain, 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 QuickMist 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 apply, talk to your doctor, nurse or pharmacist.

**▲ Important information about some of the ingredients**

Nicorette QuickMist contains small amounts of ethanol (alcohol), less than 100 mg per spray.

**▲ 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 mouthspray 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 mouthspray 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.

**3 How and when to use this medicine**

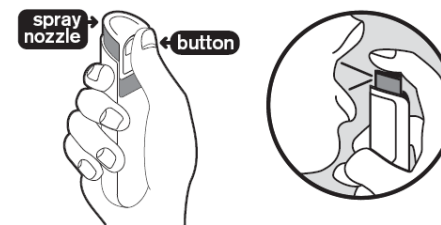
Follow the instructions and study the pictures below to ensure you use nicorette QuickMist correctly.

**TO UNLOCK NOZZLE**



**1 Opening Nicorette QuickMist**

1. Use your thumb to slide down the button (a) until it can be pushed lightly inwards (b). Do not push too hard.
2. While pushing in, slide upwards (c) to unlock the top of the dispenser. Then release the button.



**1 Priming Nicorette QuickMist**

If you are using nicorette QuickMist for the first time or if you have not

used the spray for 2 days, you must first prime the spray pump.

- Point the spray safely away from you and any other adults, children or pets that are near you.
- Press the top of the QuickMist with your index finger 3 times until a fine spray appears.

Note: priming reduces the number of sprays you may get from nicorette QuickMist.

**1 How to use Nicorette QuickMist**

3. Point the spray nozzle towards your open mouth and hold it as close to your mouth as possible.
4. Press the top of the dispenser to release one spray into your mouth. Do not inhale while spraying to avoid getting spray down your throat. For best results, do not swallow for a few seconds after spraying.

**TO LOCK NOZZLE**



**1 How to close Nicorette QuickMist**

5. Slide the button down (d) until it can be pushed inwards (e)
6. While pushing in, slide the top of the dispenser downwards (f). Release the button. The QuickMist spray is now closed.

turn over →



650975

Close the QuickMist spray every time after use to prevent use of the spray by children and accidental spraying.

- ▲ Care should be taken not to spray the eyes whilst administering the mouthspray. **If you get spray in your eye(s), rinse thoroughly with water.**
- ▲ **Do not eat or drink when administering the mouthspray.**

**① When to use Nicorette QuickMist**

If you are able to stop smoking you should use the mouthspray, when needed, in place of cigarettes. As soon you can (this could be after a number of weeks or months) you should reduce the number of sprays 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 mouthspray. There are toxins in cigarettes that can cause harm to your body. Nicorette QuickMist 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 mouthspray 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 the mouthspray but are finding this difficult you should contact your doctor, nurse or pharmacist for advice.

**① Below is the dosage information for nicorette mouthspray**

**① Children and Adolescents under 12 years**

Do not give this product to children under 12 years.

**① Adults and children aged 12 years and over**

Age	Dosage
Adults and children aged 12 years and over	<ul style="list-style-type: none"> <li>■ It is important to use enough nicotine spray to control cravings.</li> <li>■ Use one spray first when you would normally smoke a cigarette or have cravings to smoke.</li> <li>■ If your cravings do not disappear within a few minutes use a second spray.</li> <li>■ If 2 sprays are required to control cravings, future doses may be delivered as 2 consecutive sprays.</li> <li>■ Most smokers will require 1 - 2 sprays every 30 minutes to 1 hour.</li> <li>■ Do not use more than 2 sprays per dose or 4 sprays every hour. Do not use more than 64 sprays per day – this is equivalent to 4 sprays per hour for 16 hours.</li> </ul>
<ul style="list-style-type: none"> <li>■ Do not use more than 2 sprays per dose or more than 64 sprays per day – this is equivalent to 4 sprays every hour for 16 hours.</li> </ul>	

**▲ If you have used too much Nicorette QuickMist**

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

- **If you do get 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 Nicorette QuickMist**

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

**Nicotine inhalation or ingestion by a child may result in severe poisoning.**

**4 Possible side-effects**

Like all medicines, nicorette QuickMist 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 QuickMist before you are ready to reduce your nicotine intake.

**① These effects include:**

- irritability or aggression
- impatient or frustrated
- 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

**Side-effects for Nicorette QuickMist**

**Very common side-effects:** (more than 1 in every 10 people are affected)

- throat and mouth irritation
- a change in the way things taste
- headache
- feeling sick (nausea), vomiting and indigestion
- increased salivation

- burning lips
- dry mouth
- hiccups
- tingling sensation in the mouth
- Inflammation of the lining of the mouth

#### Common side-effects:

*(less than 1 in every 10 people are affected)*

- dizziness
- tingling sensation (pins and needles)
- palpitations
- cough
- mouth ulcers and bleeding gums
- toothache
- throat numbness

#### Uncommon side-effects:

*(less than 1 in every 100 people are affected)*

- difficulty sleeping or feeling restless
- feeling angry or anxious
- increased tear production or blurred vision
- hot flushes
- dry throat or skin
- runny nose
- stomach pain or discomfort and increased wind
- chest pain or discomfort
- feeling tired or irritable
- increased sweating
- rash

- pain in muscles or joints
- throat tightness

#### The following side-effects may also occur:

- abnormal beating of the heart
- difficulty in breathing e.g shortness of breath

- **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 QuickMist 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 above 25°C.
- Do not use nicorette QuickMist after the 'Use before' date shown on the back on the pack.
- Dispose of used nicorette QuickMist sensibly and 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. Other ingredients are: propylene glycol, anhydrous ethanol, trometamol, poloxamer 407, glycerol, sodium hydrogen carbonate, levomenthol, mint flavour, cooling flavour, sucralose, acesulfame potassium, hydrochloric acid, purified water.

#### What the medicine looks like

Nicorette QuickMist consists of a plastic bottle of solution held in a dispenser with a mechanical spray pump.

Each bottle contains 13.2 ml of solution which provides at least 150 sprays, each spray containing 1mg nicotine.

Nicorette QuickMist is supplied in packs of either 1 or 2 dispensers. Not all pack sizes may be marketed.

#### Who makes Nicorette QuickMist?

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.



**nicorette**<sup>®</sup>  
QuickMist  
1mg/spray mouthspray  
nicotine

Batch No:

Use before:

13.2 ml oromucosal (mouth) spray containing 1mg/spray nicotine. Delivers at least 150 sprays, each containing 1 mg of nicotine. Read the enclosed leaflet for instructions. May initially cause mouth and throat irritation. Keep out of reach and sight of children. Do not store above 25°C. For oral use only.  
McNeil Products Ltd,  
Maidenhead, Berkshire,  
SL6 3UG, UK

PL 15513/0357



613684



**nicorette**<sup>®</sup>  
QuickMist  
1mg/spray mouthspray  
nicotine

freshmint



613677

*for fast craving relief*


**QuickMist**

**freshmint**



**nicorette**<sup>®</sup>  
QuickMist  
1 mg/spray  
mouthspray  
nicotine

**1x150**  
sprays of oromucosal  
(mouth) spray



770002

# nicorette<sup>®</sup> QuickMist 1 mg/spray mouthspray nicotine

**Use:** Nicorette QuickMist 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. It provides a safer alternative to smoking for both the individual and those around them. Ideally you should aim to stop smoking. However it 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 to cut down the number of cigarettes you smoke. It may also help increase your motivation to quit.

**Directions:** For adults and children 12 years and over. It is important to use enough nicotine spray to control cravings, and using 1 or 2 sprays corresponds to the nicotine from a cigarette.

Use one spray first and if your cravings do not disappear within a few minutes use a second spray. If 2 sprays are required to control cravings, future doses may be delivered as 2 consecutive sprays.

For many smokers this means about 1-2 sprays every 30 minutes to 1 hour. Do not use more than 2 sprays per dose or 4 sprays per hour or 64 sprays per day.

Before use, please read the information leaflet carefully.

**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. May initially cause mouth and throat irritation. Do not use if you are allergic to any of the ingredients listed below. Contains ethanol.

# nicorette® QuickMist 1mg/spray mouthspray nicotine

**Use:** Nicorette QuickMist 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. It provides a safer alternative to smoking for both the individual and those around them. Ideally you should aim to stop smoking. However it 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 to cut down the number of cigarettes you smoke. It may also help increase your motivation to quit.

**Directions:** For adults and children 12 years and over. It is important to use enough nicotine spray to control cravings, and using 1 or 2 sprays corresponds to the nicotine from a cigarette.

Use one spray first and if your cravings do not disappear within a few minutes use a second spray. If 2 sprays are required to control cravings, future doses may be delivered as 2 consecutive sprays.

For many smokers this means about 1-2 sprays every 30 minutes to 1 hour. Do not use more than 2 sprays per dose or 4 sprays per hour or 64 sprays per day.

Before use, please read the information leaflet carefully.

**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. May initially cause mouth and throat irritation. Do not use if you are allergic to any of the ingredients listed below. Contains ethanol.

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 1 dispenser, containing 13.2 ml of solution which provides at least 150 oromucosal sprays, each spray containing 1mg nicotine. Other ingredients are: propylene glycol, anhydrous ethanol, trometamol, poloxamer 407, glycerol, sodium hydrogen carbonate, levomenthol, mint flavour, cooling flavour, sucralose, acesulfame potassium, hydrochloric acid, purified water.

**Storage:** Keep out of reach and sight of children. Do not store above 25°C. Dispose of sensibly. Please read the enclosed leaflet for instructions.

**ActiveStop®**  
supporting you, body & mind

*Through interactive support, we'll be there to coach you until you've stopped smoking!*



McNeil Products Ltd,  
Maidenhead, Berkshire,  
SL6 3UG, UK.

PL 15513/0357  
770011

Batch No:



Use before:



## How to open the QuickMist mouthspray | To UNLOCK NOZZLE



1. Use your thumb to slide down the button (a) until it can be pushed lightly inwards (b). Do not push too hard.
2. While pushing in, slide upwards (c) to unlock the top of the dispenser. Then release the button.

## How to prime QuickMist mouthspray



When you use the mouthspray for the first time you must first load the spray pump. Point the spray nozzle safely away from you, any other adults, children or pets near you. Press the top of the QuickMist with your index finger. Press 3 times until a fine spray appears. If you do not use the spray for 2 days, this loading procedure will need to be repeated.

## How to use the QuickMist mouthspray



3. Point the spray nozzle towards your open mouth and hold it as close to your mouth as possible.
4. Press the top of the QuickMist to release one spray into your mouth. To avoid getting spray down your throat do not inhale while spraying. For best results, do not swallow for a few seconds after spraying.

## How to close the QuickMist mouthspray | To LOCK NOZZLE




5. Slide the button down (d) until it can be pushed inwards (e).
6. While pushing in, slide the top of the dispenser downwards (f). Release the button. The QuickMist mouthspray is now closed. To take another dose repeat the steps above.

*Close the QuickMist mouthspray every time after use to prevent use of the spray by children and accidental spraying. If you get spray in your eye, rinse thoroughly with water.*

*for fast craving relief*

**QuickMist**

**freshmint**



**SAMPLE PACK  
NOT FOR RESALE**

**nicorette**<sup>®</sup>  
QuickMist  
1mg/spray  
mouthspray  
nicotine<sup>™</sup>

**1x150**  
sprays of oromucosal  
(mouth) spray

100594



100594





**nicorette**<sup>®</sup> QuickMist 1 mg/spray  
mouthspray  
nicotine

**Use:** Nicorette QuickMist 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. It provides a safer alternative to smoking for both the individual and those around them. Ideally you should aim to stop smoking. However it 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 to cut down the number of cigarettes you smoke. It may also help increase your motivation to quit.

**Directions:** For adults and children 12 years and over. It is important to use enough nicotine spray to control cravings, and using 1 or 2 sprays corresponds to the nicotine from a cigarette.

Use one spray first and if your cravings do not disappear within a few minutes use a second spray. If 2 sprays are required to control cravings, future doses may be delivered as 2 consecutive sprays.

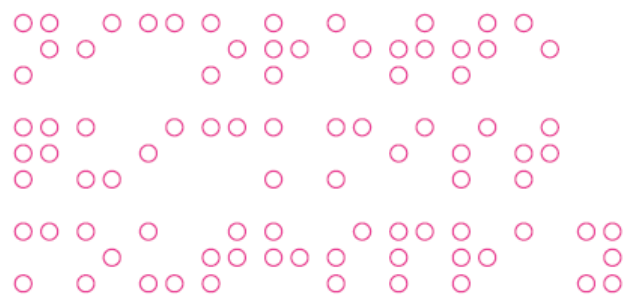
For many smokers this means about 1-2 sprays every 30 minutes to 1 hour.


Do not use more than 2 sprays per dose or 4 sprays per hour or 64 sprays per day. Before use, please read the information leaflet carefully.

**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. May initially cause mouth and throat irritation. Do not use if you are allergic to any of the ingredients listed below.  
Contains ethanol.

Braille:

<p><b>nicorette quickmist mouthspray</b></p>	
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**QuickMist 1mg/spray**  
mouthspray  
nicotine

**Use:** Nicorette QuickMist 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. It provides a safer alternative to smoking for both the individual and those around them. Ideally you should aim to stop smoking. However it 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 to cut down the number of cigarettes you smoke. It may also help increase your motivation to quit.

**Directions:** For adults and children 12 years and over. It is important to use enough nicotine spray to control cravings, and using 1 or 2 sprays corresponds to the nicotine from a cigarette.  
Use one spray first and if your cravings do not disappear within a few minutes use a second spray. If 2 sprays are required to control cravings, future doses may be delivered as 2 consecutive sprays.  
For many smokers this means about 1-2 sprays every 30 minutes to 1 hour.  
Do not use more than 2 sprays per dose or 4 sprays per hour or 64 sprays per day.  
Before use, please read the information leaflet carefully.

**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. May initially cause mouth and throat irritation. Do not use if you are allergic to any of the ingredients listed below.  
Contains ethanol.

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 2 dispensers, each containing 13.2 ml of solution which provides at least 150 oromucosal sprays, each spray containing 1mg nicotine. Other ingredients are: propylene glycol, anhydrous ethanol, trometamol, poloxamer 407, glycerol, sodium hydrogen carbonate, levomenthol, mint flavour, cooling flavour, sucralose, acesulfame potassium, hydrochloric acid, purified water.

**Storage:** Keep out of reach and sight of children. Do not store above 25°C. Dispose of sensibly. Please read the enclosed leaflet for instructions.

**ActiveStop®** *Through interactive support, we'll be there to coach you until you've stopped smoking!*  
supporting you, body & mind


Batch No:

Use before:



McNeil Products Ltd,  
Maidenhead, Berkshire,  
SL6 3UG, UK.

PL 15513/0357  
770012



3 574660 619812

**How to open the QuickMist mouthspray | To UNLOCK NOZZLE**



1. Use your thumb to slide down the button (a) until it can be pushed lightly inwards (b). Do not push too hard.
2. While pushing in, slide upwards (c) to unlock the top of the dispenser. Then release the button.

**How to prime QuickMist mouthspray**



When you use the mouthspray for the first time you must first load the spray pump. Point the spray nozzle safely away from you, any other adults, children or pets near you. Press the top of the QuickMist with your index finger. Press 3 times until a fine spray appears. If you do not use the spray for 2 days, this loading procedure will need to be repeated.

**How to use the QuickMist mouthspray**



3. Point the spray nozzle towards your open mouth and hold it as close to your mouth as possible.
4. Press the top of the QuickMist to release one spray into your mouth. To avoid getting spray down your throat do not inhale while spraying. For best results, do not swallow for a few seconds after spraying.

**How to close the QuickMist mouthspray | To LOCK NOZZLE**



5. Slide the button down (d) until it can be pushed inwards (e).
6. While pushing in, slide the top of the dispenser downwards (f). Release the QuickMist mouthspray is now closed. To take another dose repeat the steps above.

*Close the QuickMist mouthspray every time after use to prevent use of the spray by children and accidental spraying. If you get spray in your eye, rinse thoroughly with water.*