UKPAR Nicorette Cools 2 mg Lozenge
Nicorette Cools 4 mg Lozenge
(nicotine resinate)
PL 15513/0374-5

UKPAR

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LAY SUMMARY

On 27 February 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted McNeil Products Limited Marketing Authorisations for the medicinal products Nicorette Cools 2 mg and 4 mg Lozenge (PL 15513/0374-5). These products are General Sales List (GSL) medicines, which means that they are available without prescription and do not have to be purchased under the supervision of a pharmacist.

Nicorette Cools 2 mg and 4 mg Lozenge contain the active ingredient nicotine (as nicotine resinate), which is absorbed through the lining of the mouth. These medicines are used to relieve and/or prevent withdrawal symptoms and reduce the cravings smokers (including pregnant or breast-feeding women) get when they try to stop smoking or to reduce the number of cigarettes they smoke.

Nicorette Cools 2 mg and 4 mg Lozenge can also be used at those times when a smoker cannot or does not want to smoke, for example:
• to avoid harm to others, such as, children or family.
• in smoke-free areas, such as pub, work, public transport, e.g aeroplanes.

Nicorette Cools Lozenge is a Nicotine Replacement Therapy (NRT).

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Nicorette Cools 2 mg and 4 mg Lozenge outweigh the risks; hence Marketing Authorisations have been granted.
NICORETTE COOLS 2 MG LOZENGE
NICORETTE COOLS 4 MG LOZENGE
(nicotine resinate)
PL 15513/0374-5

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted McNeil Products Limited Marketing Authorisations for the medicinal products Nicorette Cools 2 mg and 4 mg Lozenge (PL 15513/0374-5) on 27 February 2012. These products are General Sales Licence (GSL) medicines, which relieve and/or prevent craving and nicotine withdrawal symptoms associated with tobacco dependence. Nicorette Cools 2 mg and 4 mg Lozenge are indicated:

- to aid smokers wishing to quit or reduce prior to quitting. Nicorette Cools 2 mg and 4 mg Lozenge are also indicated in pregnant and lactating women making a quit attempt.
- to assist smokers who are unwilling or unable to smoke
- as a safer alternative to smoking for smokers and those around them.

These are national abridged complex applications, submitted under Article 8.3 of Directive 2001/83/EC, as amended, as line extensions (the addition of a new pharmaceutical form) to Nicorette 2mg and 4mg Medicated Chewing Gum (PL 15513/0169-70, McNeil Products Limited) first authorised in the UK on 14 May 1992. The proposed formulations provide similar plasma concentrations of nicotine to the original gum formulations, albeit via a different pharmaceutical form however by the same route of administration (absorption through buccal mucosa).

The active ingredient nicotine (as nicotine resinate) belongs to the pharmacotherapeutic group ‘drugs used in nicotine dependence (N07B A01)’. Nicotine is an agonist at nicotine receptors in the peripheral and central nervous system and has pronounced CNS and cardiovascular effects.

No new non-clinical have been submitted, which is acceptable given that nicotine is a widely used, well-known active substance that has been in clinical use for many years

To support these applications, the applicant has submitted a Phase 1 clinical (bioequivalence) study comparing the pharmacokinetics of the test Nicotine Strongmint Lozenge 2mg and 4mg versus the reference products NiQuitin™ lozenge 2mg and 4 mg. During product development, Nicotine Strongmint Lozenge was the name used for the Nicorette Cools Lozenge products. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

No new or unexpected safety concerns arose during review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Nicorette Cools 2 mg and 4 mg Lozenge outweigh the risks and Marketing Authorisations were granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
INN: Nicotine resinate
Chemical Name: 2-methyl-2-propenoic acid, polymer with diethenylbenzene, compd. with (S)-3-(1-methyl-2-pyrrolidinyl)pyridine
Appearance: White or slightly yellowish powder
Solubility Practically insoluble in water.

Nicotine resinate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance nicotine resinate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT
Other Ingredients
Other ingredients consist of the pharmaceutical excipients in the lozenge core and coating, namely mannitol (E421), xanthan gum (E415), Winterfresh flavour, sodium carbonate anhydrous, sucralose (E955), acesulfame potassium (E950), magnesium stearate (E470b), hypromellose (Methocel E3), titanium dioxide (E171), Sepifilm gloss and polysorbate 80. Appropriate justifications for the inclusion of each excipient have been provided.

All the excipients comply with their respective European Pharmacopoeia monograph with the exception of sucralose, Winterfresh flavour and Sepifilm gloss. Sucralose is controlled to its United States Pharmacopoeial-National Formulary specification. Winter fresh flavour and Septifilm gloss are controlled to suitable in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, stable lozenges containing 2 mg and 4mg of nicotine resinate bioequivalent to the reference products NiQuitin™ 2mg and 4 mg Mint Lozenge

Suitable pharmaceutical development data have been provided for these applications.

Satisfactory in-vitro dissolution profiles have been provided for these products.
Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated on pilot-scale batches and shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on the first three full-scale production batches of each strength prior to marketing.

Control of Finished Product
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System
Both strengths of the lozenges are packaged in either:
1. polypropylene containers, containing silica dessicant (‘Flip-pack’) in pack sizes of 20 (1x20) and 80 (4x20) lozenges.
2. orientated polyamide/aluminium/polyvinyl chloride (OPA/Al/PVC) blisters in a pack sizes of 24 (2x12) lozenges.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months, with no special storage conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence (Phase I clinical) study.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are satisfactory from a pharmaceutical perspective. The Marketing Authorisation Holder has committed to submitting mock-ups to the regulatory authorities for approval before marketing any pack size.
A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA (Marketing Authorisation Application) Forms**

The MAA forms are pharmaceutically satisfactory.

**Expert Report (Quality Overall Summary)**

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

**Conclusion**

The grant of Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of nicotine are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT (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.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these products are line extensions of known active substance products, intended for indications currently treated with Nicorette 2 mg and 4 mg Medicated Chewing Gum (McNeil Products Limited), no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of Marketing Authorisations is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of nicotine is well-known. With the exception of data from the bioequivalence (Phase I clinical) study described below, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

Pharmacokinetics
In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study:

A randomised, single-dose, open-label, crossover study comparing the pharmacokinetics of the test products Nicotine Strongmint Lozenge 2mg, with low level of buffer capacity (McNeil Products Limited) and Nicotine Strongmint Lozenge 4mg, with medium level of buffer capacity (McNeil Products Limited) versus the reference products Nicotinex\textsuperscript{TM} Lozenge 2 mg and 4 mg in healthy smokers. The study also investigated the pharmacokinetic profile of two prototype formulations of Nicotine Strongmint Lozenge 4mg that contained either lower or higher levels of buffer than Nicotine Strongmint Lozenge 4mg, with medium level buffer.

**Table S1 Investigational Products and Identity**

<table>
<thead>
<tr>
<th>Investigational Product</th>
<th>Form</th>
<th>Route</th>
<th>Nicotine Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSL2L</td>
<td>Lozenge</td>
<td>Oral*</td>
<td>2 mg</td>
</tr>
<tr>
<td>NiQuitin\textsuperscript{TM}</td>
<td>Lozenge</td>
<td>Oral*</td>
<td>2 mg</td>
</tr>
<tr>
<td>NSL4M</td>
<td>Lozenge</td>
<td>Oral*</td>
<td>4 mg</td>
</tr>
<tr>
<td>NiQuitin\textsuperscript{TM}</td>
<td>Lozenge</td>
<td>Oral*</td>
<td>4 mg</td>
</tr>
<tr>
<td>NSL4L</td>
<td>Lozenge</td>
<td>Oral*</td>
<td>4 mg</td>
</tr>
<tr>
<td>NSL4H</td>
<td>Lozenge</td>
<td>Oral*</td>
<td>4 mg</td>
</tr>
</tbody>
</table>

NSL2L=Nicotine Strongmint Lozenge 2mg, with low level of buffer capacity
NSL4M=Nicotine Strongmint Lozenge 4mg, with medium level of buffer capacity
NSL4L=Nicotine Strongmint Lozenge 4mg, with low level of buffer capacity
NSL4H=Nicotine Strongmint Lozenge 4mg, with high level of buffer capacity

*In contrast to customary terminology, oral route of administration in this study does not entail the swallowing of the lozenge but a complete dissolution in the oral cavity

Number of subjects studied:
One-hundred and four (104) adult healthy volunteers (52 males and 52 females) were planned and included in the study. One-hundred (100) completed the study.

Dose administered (test/reference)
One-hundred (100) subjects received five single doses of the investigational products Nicotine Strongmint Lozenge 2mg, with low level of buffer capacity [NSL2L], NiQuitin\textsuperscript{TM} Lozenge 2mg, Nicotine Strongmint Lozenge 4mg, with medium level of buffer capacity [NSL4M], NiQuitin\textsuperscript{TM} Lozenge 4mg and either of Nicotine Strongmint Lozenge 4 mg, with low level of buffer capacity [NSL4L] or Nicotine Strongmint Lozenge 4 mg, with high level of buffer capacity [NSL4H] on separate treatment visits. Four subjects did not receive all doses (two subjects due to pregnancy, one...
subject was withdrawn due to poor compliance, and one subject discontinued because he/she was no longer willing to participate).

**Primary Objective:**
The primary objective of the study was to demonstrate bioequivalence between NSL2L and NiQuitin™ Lozenge 2 mg, and between NSL4M and NiQuitin™ Lozenge 4 mg.

Bioequivalence criteria
The protocol defines acceptance criteria of 0.8 – 1.25 for both AUC and $C_{max}$. This is satisfactory.

Duration of sampling following dosing
At treatment visits, blood samples for pharmacokinetic analyses (of nicotine in plasma) were drawn before and at 7.5, 15, 20, 30, 40, 50, and 60 minutes, as well as at 1.25, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after start of drug administration.

Washout period
Periods of at least 36 hours separated the treatment visits. This period is sufficient to prevent carryover effect.

Method of data analysis
An analysis of variance (ANOVA) model encompassing subject (considered random and nested in sequence), period, sequence, treatment and site was fitted to the data after logarithmic transformation of baseline corrected $C_{max}$, AUCt, and AUC$\infty$. For the response parameters, bioequivalence was concluded if the 90% confidence interval (CI) for the corresponding comparison test/standard was entirely within the equivalence interval (80%-125%).

Results:

<table>
<thead>
<tr>
<th>Table S2</th>
<th>Pharmacokinetic Parameters for the 2 mg Products (Mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>n</td>
</tr>
<tr>
<td>NSL2L</td>
<td>94</td>
</tr>
<tr>
<td>NiQuitin™ Lozenge 2 mg</td>
<td>96</td>
</tr>
</tbody>
</table>

SD=standard deviation

<table>
<thead>
<tr>
<th>Table S3</th>
<th>Pharmacokinetic Parameters for the 4 mg Products (Mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>n</td>
</tr>
<tr>
<td>NSL4L</td>
<td>46</td>
</tr>
<tr>
<td>NSL4M</td>
<td>97</td>
</tr>
<tr>
<td>NSL4H</td>
<td>50</td>
</tr>
<tr>
<td>NiQuitin™ Lozenge 4 mg</td>
<td>99</td>
</tr>
</tbody>
</table>

SD= standard deviation
The 90% confidence interval (CI) for the test/reference lie within the acceptance criteria of 80-125% for NSL2L and NSL4M formulations

Assessor’s Conclusion on Bioequivalence
Bioequivalence has been demonstrated between the NSL2L and NiQuitin™ Lozenge 2mg and between NSL4M and NiQuitin™ Lozenge 4mg.

Furthermore, the pharmacokinetic parameters of NSL 2mg and 4 mg are within the levels of currently marketed oral Nicorette products (lozenges, gum, inhalator and sublingual tablets). The difference of pharmacokinetic (PK) profile between the different Nicorette products is expected to be of little clinical significance for a product, which is self-titrated to a subject’s needs by frequency of dosing.

Efficacy
The efficacy of nicotine is well-known. No new efficacy data have been submitted and none are required for applications of this type.

Safety
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for applications of this type, as the overall safety profile of nicotine is well-known. No new or unexpected safety issues were raised by the pharmacokinetic data.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are clinically acceptable. The SmPCs are consistent with those for Nicorette 2mg and 4mg Medicated Chewing Gum. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

Clinical Expert Report (Clinical Overview)
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.
PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

CONCLUSION
The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Nicorette Cools 2 mg and 4 mg Lozenge are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of nicotine are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new efficacy data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s 2mg and 4mg strength lozenges and NiQuitin™ Lozenge 2 mg and 4 mg.

Furthermore, the pharmacokinetic parameters of NSL 2mg and 4 mg are within the levels of currently marketed oral Nicorette products (lozenges, gum, inhalator and sublingual tablets). The difference of pharmacokinetic (PK) profile between the different Nicorette products is expected to be of little clinical significance for a product, which is self-titrated to a subject’s needs by frequency of dosing.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for applications of this type. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are acceptable. The SmPCs are consistent with those for Nicorette 2mg and 4mg Medicated Chewing Gum. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with nicotine is considered to have demonstrated the therapeutic value of the products. The benefit/risk balance is, therefore, considered to be positive.
NICORETTE COOLS 2 MG LOZENGE
NICORETTE COOLS 4 MG LOZENGE
(nicotine resinate)
PL 15513/0374-5

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation applications on 22 December 2010.

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 04 February 2011.

3 Following assessment of the applications the MHRA requested further information relating to the clinical dossier on 23 March 2011 and on the quality dossier on 04 April 2011 and 08 September 2011.

4 The applicant responded to the MHRA’s requests, providing further information on the clinical dossier on 15 August 2011 and on the quality dossier on 15 August 2011, 16 December 2011, 22 December 2011 and 12 January 2012.

5 The applications were granted on 27 February 2012.
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Nicorette Cools 2 mg Lozenge

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each lozenge contains 2 mg nicotine (as nicotine resinate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Compressed lozenge.

An oval, white to off-white lozenge imprinted with a “n” on one side and “2” on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Nicorette Cools 2 mg Lozenge relieves and/or prevents craving and nicotine withdrawal symptoms associated with tobacco dependence. It is indicated to aid smokers wishing to quit or reduce prior to quitting, to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them.

Nicorette Cools 2 mg Lozenge is indicated in pregnant and lactating women making a quit attempt.

4.2 Posology and method of administration
Nicorette Cools 2 mg Lozenge is suitable for smokers who smoke 20 or less cigarettes per day.

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

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

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

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

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

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

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

4.3 Contraindications
Hypersensitivity to any of components of the lozenge.
Nicorette Cools Lozenge is contraindicated in children under the age of 12 years.
4.4 Special warnings and precautions for use

Any risks which may be associated with the use of NRT are substantially outweighed in virtually all circumstances by the well established dangers of continued smoking.

**Underlying cardiovascular disease:** In stable cardiovascular disease Nicorette Cools Lozenge presents a lesser hazard than continuing to smoke. However dependent smokers currently hospitalised as a result of myocardial infarction, severe dysrhythmia or cerebrovascular accident and who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions. If this fails, Nicorette Cools Lozenge may be considered, but as data on safety in this patient group are limited, initiation should only be under medical supervision.

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

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

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

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, Pregnancy and lactation

**Pregnancy**

Stopping smoking is the single most effective intervention for improving the health of both the pregnant smoker and her baby, and the earlier abstinence is achieved the better. Ideally smoking cessation during pregnancy should be achieved without NRT. However, if the mother cannot (or is considered unlikely to) quit without pharmacological support, NRT may be used as the risk to the foetus is lower than that expected with smoking tobacco. Stopping completely is by far the best option but if this is not achievable Nicorette Cools 2 mg Lozenge may be used in pregnancy as a safer alternative to smoking. Because of the potential for nicotine-free periods, intermittent dose forms are preferable, but patches may be necessary if there is significant nausea and/or vomiting. If patches are used they should, if possible, be removed at night when the foetus would not normally be exposed to nicotine.
**Lactation**

The relatively small amounts of nicotine found in breast milk during NRT use are less hazardous to the infant than second-hand smoke. Intermittent dose forms would minimize the amount of nicotine in breast milk and permit feeding when levels were at their lowest.

### 4.7 Effects on ability to drive and use machines

Not applicable.

### 4.8 Undesirable effects

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

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

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

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

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

<table>
<thead>
<tr>
<th>Nervous system disorders:</th>
<th>Very common:</th>
<th>Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td>Dizziness</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders:</th>
<th>Very common:</th>
<th>Nausea, gastrointestinal discomfort, hiccups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td>Vomiting</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions:</th>
<th>Very common:</th>
<th>Sore mouth or throat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare:</td>
<td>Allergic reactions including angioedema</td>
<td></td>
</tr>
</tbody>
</table>

| Respiratory, thoracic and mediastinal disorders:       | Common:     | Coughing             |

<table>
<thead>
<tr>
<th>Cardiac disorders:</th>
<th>Uncommon:</th>
<th>Palpitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare:</td>
<td>Reversible atrial fibrillation</td>
<td></td>
</tr>
</tbody>
</table>

| Skin and subcutaneous tissue disorders: | Uncommon: | Erythema, urticaria |

### 4.9 Overdose

**Symptoms** The minimum lethal dose of nicotine in a non-tolerant man has been estimated to be 40 to 60 mg. Symptoms of acute nicotine poisoning include nausea, 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 terminal convulsions.
Management of an overdose: All nicotine intake should stop immediately and the patient should be treated symptomatically. Artificial respiration should be instituted if necessary. Activated charcoal reduces the gastro-intestinal absorption of nicotine.

5 Pharmacological Properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Drug used in nicotine dependence.
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.

Abrupt cessation of the use of tobacco-containing products following a prolonged period of daily use results in a characteristic withdrawal syndrome that includes four or more of the following: dysphoria or depressed mood; insomnia; irritability, frustration or anger; anxiety; difficulty concentrating, restlessness or impatience; decreased heart rate; and increased appetite or weight gain. Nicotine craving is an important element in the withdrawal syndrome after smoking cessation.

Clinical studies have shown that nicotine replacement products can help smokers abstain from smoking by relieving these withdrawal symptoms.

Increased appetite is a recognised symptom of nicotine withdrawal and post-cessation weight gain is common. Clinical trials have demonstrated that Nicotine Replacement Therapy can help control weight following a quit attempt.

A bioequivalence study for Nicorette Cools 2mg and 4mg Lozenges measured relief in urges to smoke (i.e. craving relief) at specified intervals after the start of study drug administration.

Study subjects rated urges to smoke using a scale with 4 ordered categories:
1. No or very light urge to smoke (0-25% of maximum urge conceivable)
2. Noticeable urge to smoke (25%-50% of maximum urge conceivable)
3. Disturbing urge to smoke (50%-75% of maximum urge conceivable)
4. Very strong or extreme urge to smoke (75%-100% of maximum urge conceivable)

The data below presents urges to smoke data obtained for Nicorette Cools 2 mg Lozenge in 94 subjects, before and at 2, 5 and 10 minutes after start of treatment administration.

<table>
<thead>
<tr>
<th>How strong was your urge to smoke?</th>
<th>Before start of administration of study treatment</th>
<th>After 2 minutes</th>
<th>After 5 minutes</th>
<th>After 10 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1 (No or very light urge to smoke)</td>
<td>0 (0%)</td>
<td>14 (17.5%)</td>
<td>36 (45%)</td>
<td>50 (62.5%)</td>
</tr>
<tr>
<td>Category 2 – Category 4</td>
<td>80 (100%)</td>
<td>66 (82.5%)</td>
<td>44 (55%)</td>
<td>30 (37.5%)</td>
</tr>
</tbody>
</table>

Table 2: Subjects who experienced any relief in urges to smoke (number and percent)

<table>
<thead>
<tr>
<th>Any relief in urges to smoke?</th>
<th>Before start of administration of study treatment</th>
<th>After 2 minutes</th>
<th>After 5 minutes</th>
<th>After 10 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>0 (0%)</td>
<td>36 (45%)</td>
<td>68 (85%)</td>
<td>75 (93.75%)</td>
</tr>
<tr>
<td>No</td>
<td>80 (100%)</td>
<td>44 (55%)</td>
<td>12 (15%)</td>
<td>5 (6.25%)</td>
</tr>
</tbody>
</table>

5.2 Pharmacokinetic properties
Absorption
A Nicotine Cools Lozenge dissolves completely, typically in 10-20 minutes. Assuming complete dissolution in the mouth, most of its nicotine is absorbed through the oral mucosa. This fraction is almost entirely delivered to the systemic circulation. The remaining nicotine
released in the mouth is swallowed and undergoes considerable first-pass metabolism in the intestine and liver. As a consequence, only a small part of the total nicotine given with a lozenge reaches the circulation via the intestine.

5 ng/mL is achieved after a single-dose of the Nicotine Cools Lozenge 2 mg, and about 8 ng/mL after a single-dose of the Nicotine Cools Lozenge 4 mg. Area under the time vs. plasma concentration curve extrapolated to infinity (AUC$_\infty$) after a single-dose of a Nicotine Cools Lozenge 2 mg is about 16 h*ng/mL, and about 31 h*ng/mL after a single-dose of a Nicotine Cools Lozenge 4 mg.

**Distribution**
The volume of distribution following intravenous administration of nicotine is about 2 to 3 l/kg.

Plasma protein binding of nicotine is less than 5%. Therefore, changes in nicotine binding from use of concomitant drugs or alterations of plasma proteins by disease states would not be expected to have any significant effects on the nicotine pharmacokinetics.

**Biotransformation**
The major eliminating organ is the liver, although the kidney and lung also metabolise nicotine. More than 20 metabolites of nicotine have been identified, all of which are believed to be less active than the parent compound.

The primary metabolite of nicotine in plasma, cotinine, has a terminal half-life of 15 to 20 hours and concentrations that exceed nicotine by 10-fold.

**Elimination**
The average plasma clearance is about 70 l/h and the elimination half-life is approximately 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, but as much as 30% of nicotine may be excreted unchanged with high flow rates and acidification of the urine below pH 5.

**Characteristics in specific groups of subjects**

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

**Hepatic Impairment**
The pharmacokinetics of nicotine is unaffected in individuals with liver cirrhosis and mild liver impairment (Child-Pugh score 5), and decreased by 40-50% in subjects with moderate liver impairment (Child-Pugh score 7). There is no information available in subjects with a Child-Pugh score > 7.

A minor reduction in total clearance of nicotine has been demonstrated in healthy elderly subjects, however not justifying adjustment of dosage.

**5.3 Preclinical safety data**
Preclinical data indicate that nicotine is neither mutagenic nor genotoxic. There are no other findings derived from preclinical testing of relevance to the prescriber in determining the safety of the product which have not been considered in other relevant sections of this Summary of Product Characteristics.
6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Core
Mannitol (E421)
Xanthan gum (E415)
Winterfresh Flavour
Sodium carbonate anhydrous
Sucralose (E955)
Acesulfame potassium (E950)
Magnesium stearate (E470b)

Coating
Hypermellose (Methocel E3)
Winterfresh Flavour
Titanium dioxide (E171)
Sucralose (E955)
Sepifilm gloss
Acesulfame potassium (E950)
Polysorbate 80
Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Polypropylene container with silica gel desiccant (“Flip pack”)
Pack Sizes: 20 (1x20) and 80 (4x20) lozenges.
or
OPA/Al/PVC blisters
Pack Size: 24 (2x12) lozenges.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

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

8 MARKETING AUTHORISATION NUMBER(S)
PL 15513/0374

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
27/02/2012

10 DATE OF REVISION OF THE TEXT
27/02/2012
1 NAME OF THE MEDICINAL PRODUCT
Nicorette Cools 4 mg Lozenge

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each lozenge contains 4 mg nicotine (as nicotine resinate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Compressed lozenge.

An oval, white to off-white lozenge imprinted with a “n” on one side and “4” on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Nicorette Cools 4 mg Lozenge relieves and/or prevents craving and nicotine withdrawal symptoms associated with tobacco dependence. It is indicated to aid smokers wishing to quit or reduce prior to quitting, to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them.

Nicorette Cools 4 mg Lozenge is indicated in pregnant and lactating women making a quit attempt.

4.2 Posology and method of administration
Nicorette Cools 4 mg Lozenge is suitable for smokers who smoke more than 20 cigarettes per day.

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

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

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

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

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

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

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

4.3 Contraindications
Hypersensitivity to any of components of the lozenge.
Nicorette Cools Lozenge is contraindicated in children under the age of 12 years.
4.4 Special warnings and precautions for use
Any risks which may be associated with the use of NRT are substantially outweighed in virtually all circumstances by the well established dangers of continued smoking.

Underlying cardiovascular disease: In stable cardiovascular disease Nicorette Cools Lozenge presents a lesser hazard than continuing to smoke. However dependent smokers currently hospitalised as a result of myocardial infarction, severe dysrhythmia or cerebrovascular accident and who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions. If this fails, Nicorette Cools Lozenge may be considered, but as data on safety in this patient group are limited, initiation should only be under medical supervision.

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

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

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

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction
No clinically relevant interactions between nicotine replacement therapy and other drugs have definitely been established. However nicotine may possibly enhance the haemodynamic effects of adenosine i.e. increase in blood pressure and heart rate and also increase pain response (angina-pectoris type chest pain) provoked by adenosine administration.

4.6 Fertility, Pregnancy and lactation
Pregnancy
Stopping smoking is the single most effective intervention for improving the health of both the pregnant smoker and her baby, and the earlier abstinence is achieved the better. Ideally smoking cessation during pregnancy should be achieved without NRT. However, if the mother cannot (or is considered unlikely to) quit without pharmacological support, NRT may be used as the risk to the foetus is lower than that expected with smoking tobacco. Stopping completely is by far the best option but if this is not achievable Nicorette Cools 4 mg Lozenge may be used in pregnancy as a safer alternative to smoking. Because of the potential for nicotine-free periods, intermittent dose forms are preferable, but patches may be necessary if there is significant nausea and/or vomiting. If patches are used they should, if possible, be removed at night when the foetus would not normally be exposed to nicotine.
**Lactation**

The relatively small amounts of nicotine found in breast milk during NRT use are less hazardous to the infant than second-hand smoke. Intermittent dose forms would minimize the amount of nicotine in breast milk and permit feeding when levels were at their lowest.

**4.7 Effects on ability to drive and use machines**

Not applicable.

**4.8 Undesirable effects**

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

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

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

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

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

- **Nervous system disorders:**
  - Very common: Headache
  - Common: Dizziness
- **Gastrointestinal disorders:**
  - Very common: Nausea, gastrointestinal discomfort, hiccups
  - Common: Vomiting
- **General disorders and administration site conditions:**
  - Very common: Sore mouth or throat
  - Rare: Allergic reactions including angioedema
- **Respiratory, thoracic and mediastinal disorders:**
  - Common: Coughing
- **Cardiac disorders:**
  - Uncommon: Palpitations
  - Very rare: Reversible atrial fibrillation
- **Skin and subcutaneous tissue disorders:**
  - Uncommon: Erythema, urticaria

**4.9 Overdose**

**Symptoms:** The minimum lethal dose of nicotine in a non-tolerant man has been estimated to be 40 to 60 mg. Symptoms of acute nicotine poisoning include nausea, 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 terminal convulsions.
Management of an overdose: All nicotine intake should stop immediately and the patient should be treated symptomatically. Artificial respiration should be instituted if necessary. Activated charcoal reduces the gastro-intestinal absorption of nicotine.

5

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Drug used in nicotine dependence.
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.

Abrupt cessation of the use of tobacco-containing products following a prolonged period of daily use results in a characteristic withdrawal syndrome that includes four or more of the following: dysphoria or depressed mood; insomnia; irritability, frustration or anger; anxiety; difficulty concentrating, restlessness or impatience; decreased heart rate; and increased appetite or weight gain. Nicotine craving is an important element in the withdrawal syndrome after smoking cessation.

Clinical studies have shown that nicotine replacement products can help smokers abstain from smoking by relieving these withdrawal symptoms.

Increased appetite is a recognised symptom of nicotine withdrawal and post-cessation weight gain is common. Clinical trials have demonstrated that Nicotine Replacement Therapy can help control weight following a quit attempt.

A bioequivalence study for Nicorette Cools 2mg and 4mg Lozenges measured relief in urges to smoke (i.e. craving relief) at specified intervals after the start of study drug administration.

Study subjects rated urges to smoke using a scale with 4 ordered categories:
1. No or very light urge to smoke (0-25% of maximum urge conceivable)
2. Noticeable urge to smoke (25%-50% of maximum urge conceivable)
3. Disturbing urge to smoke (50%-75% of maximum urge conceivable)
4. Very strong or extreme urge to smoke (75%-100% of maximum urge conceivable)

The data below presents urges to smoke data obtained for Nicorette Cools 4 mg Lozenge in 97 subjects, before and at 2, 5 and 10 minutes after start of treatment administration.

Table 1: Subjects who rated their urges to smoke either ‘No or very light’ or stronger (number and percent)

<table>
<thead>
<tr>
<th>How strong was your urge to smoke?</th>
<th>Before start of administration of study treatment</th>
<th>After 2 minutes</th>
<th>After 5 minutes</th>
<th>After 10 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1 (No or very light urge to smoke)</td>
<td>0 (0%)</td>
<td>20 (23.5%)</td>
<td>43 (50.5%)</td>
<td>57 (68%)</td>
</tr>
<tr>
<td>Category 2 – Category 4</td>
<td>80 (100%)</td>
<td>65 (76.5%)</td>
<td>42 (49.5%)</td>
<td>28 (32%)</td>
</tr>
</tbody>
</table>

Table 2: Subjects who experienced any relief in urges to smoke (number and percent)

<table>
<thead>
<tr>
<th>Any relief in urges to smoke?</th>
<th>Before start of administration of study treatment</th>
<th>After 2 minutes</th>
<th>After 5 minutes</th>
<th>After 10 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>0 (0%)</td>
<td>40 (47%)</td>
<td>70 (85%)</td>
<td>78 (93%)</td>
</tr>
<tr>
<td>No</td>
<td>90 (100%)</td>
<td>45 (53%)</td>
<td>15 (15%)</td>
<td>6 (7%)</td>
</tr>
</tbody>
</table>

* one observation missing
5.2 Pharmacokinetic properties

Absorption
A Nicotine Cools Lozenge dissolves completely, typically in 10-20 minutes. Assuming complete dissolution in the mouth, most of its nicotine is absorbed through the oral mucosa. This fraction is almost entirely delivered to the systemic circulation. The remaining nicotine released in the mouth is swallowed and undergoes considerable first-pass metabolism in the intestine and liver. As a consequence, only a small part of the total nicotine given with a lozenge reaches the circulation via the intestine.

A maximum nicotine plasma concentration of about 5 ng/mL is achieved after a single-dose of the Nicotine Cools Lozenge 2 mg, and about 8 ng/mL after a single-dose of the Nicotine Cools Lozenge 4 mg. Area under the time vs. plasma concentration curve extrapolated to infinity (AUC∞) after a single-dose of a Nicotine Cools Lozenge 2 mg is about 16 h*ng/mL, and about 31 h*ng/mL after a single-dose of a Nicotine Cools Lozenge 4 mg.

Distribution
The volume of distribution following intravenous administration of nicotine is about 2 to 3 l/kg.

Plasma protein binding of nicotine is less than 5%. Therefore, changes in nicotine binding from use of concomitant drugs or alterations of plasma proteins by disease states would not be expected to have any significant effects on the nicotine pharmacokinetics.

Biotransformation
The major eliminating organ is the liver, although the kidney and lung also metabolise nicotine. More than 20 metabolites of nicotine have been identified, all of which are believed to be less active than the parent compound.

The primary metabolite of nicotine in plasma, cotinine, has a terminal half-life of 15 to 20 hours and concentrations that exceed nicotine by 10-fold.

Elimination
The average plasma clearance is about 70 l/h and the elimination half-life is approximately 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, but as much as 30% of nicotine may be excreted unchanged with high flow rates and acidification of the urine below pH 5.

Characteristics in specific groups of subjects
Renal Impairment
Progressive severity of renal impairment is associated with decreased total clearance of nicotine. Nicotine clearance was decreased by on average 50% in subjects with severe renal impairment. Raised nicotine levels have been seen in smoking subjects undergoing hemodialysis.

Hepatic Impairment
The pharmacokinetics of nicotine is unaffected in individuals with liver cirrhosis and mild liver impairment (Child-Pugh score 5), and decreased by 40-50% in subjects with moderate liver impairment (Child-Pugh score 7). There is no information available in subjects with a Child-Pugh score > 7.

A minor reduction in total clearance of nicotine has been demonstrated in healthy elderly subjects, however not justifying adjustment of dosage.
5.3 Preclinical safety data
Preclinical data indicate that nicotine is neither mutagenic nor genotoxic.

There are no other findings derived from preclinical testing of relevance to the prescriber in determining the safety of the product which have not been considered in other relevant sections of this Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Core
Mannitol (E421)
Xanthan gum (E415)
Winterfresh Flavour
Sodium carbonate anhydrous
Sucralose (E955)
Acesulfame potassium (E950)
Magnesium stearate (E470b)

Coating
Hypropemellose (Methocel E3)
Winterfresh Flavour
Titanium dioxide (E171)
Sucralose (E955)
Sepifilm gloss
Acesulfame potassium (E950)
Polysorbate 80
Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Polypropylene container with silica gel desiccant (“Flip pack”)
Pack Sizes: 20 (1x20) and 80 (4x20) lozenges.
or
OPA/Al/PVC blisters
Pack Size: 24 (2x12) lozenges.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

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

8 MARKETING AUTHORISATION NUMBER(S)
PL 15513/0375
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
27/02/2012

10 DATE OF REVISION OF THE TEXT
27/02/2012
PATIENT INFORMATION LEAFLET

UKPAR Nicorette Cools 2 mg and 4 mg Lozenge

PL 15513/0374-5

What you should know about Nicorette Cools Lozenge

Do not use Nicorette Cools Lozenge if you:
- Have had an allergic reaction to it or any other of its ingredients.
- Have an oral or genital ulcer, or sore mouth.
- Have a cold sore, or sore throat.
- Are pregnant or breastfeeding.
- Are taking other medicines that affect your blood vessels or arteries.
- Have had a previous heart attack, stroke, or transient ischemic attack.
- Have glaucoma or diabetes mellitus.
- Have a history of alcoholism or drug addiction.
- Have a history of mental illness, such as depression or anxiety.
- Have a history of suicide attempts.
- Have a history of addiction to other substances.
- Have a history of drug use.

Before using this medicine

DO NOT USE Nicorette Cools Lozenge:
- If you have had an allergic reaction to any of the other ingredients.
- If you are a child under 12 years of age.
- If you are pregnant or breastfeeding.
- If you are taking other medicines that affect your blood vessels or arteries.
- If you have a cold sore, or sore throat.
- If you have glaucoma or diabetes mellitus.
- If you have a history of alcoholism or drug addiction.
- If you have a history of mental illness, such as depression or anxiety.
- If you have a history of suicide attempts.
- If you have a history of addiction to other substances.
- If you have a history of drug use.

How and when to use this medicine

How to use Nicorette Cools Lozenge

Place the lozenge in your mouth. Allow it to dissolve slowly. This will release nicotine, which may affect the balance of your body’s hormones. Nicorette Cools Lozenge should NOT be chewed or swallowed. You should not eat or drink while a lozenge is in your mouth. The number of lozenges you use each day will depend on how many cigarettes you smoked and how strong they were. Do not increase the dose above the one you should use.

When to use Nicorette Cools Lozenge

If you smoke 10 or less cigarettes a day, the 2 mg nicotine lozenge will help reduce your cravings. If you are able to stop smoking, you should use the lozenge when needed, as you would for other substitutes. If you smoke 10 or more cigarettes a day, the 4 mg nicotine lozenge will help reduce your cravings. If you are able to stop smoking, you should use the lozenge when needed, as you would for other substitutes.

PRODUCTS ARE SUPPLIED BY:

UKPAR Nicorette Cools 2 mg and 4 mg Lozenge
PL 15513/0374-5

PATIENT INFORMATION LEAFLET
UKPAR Nicorette Cools 2 mg and 4 mg Lozenge

PL 15513/0374-5

Replacement Therapy 857 .

If you are unable to stop smoking, or do not feel ready to quit at this time, you should replace one or more cigarettes with the lozenge. These are listed in the pack as "Nicorette Cools" or "Nicorette Cools 2 mg and 4 mg Lozenge". The lozenge contains nicotine, which provides a safe 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 try to stop smoking completely.

You can reduce the frequency on those occasions when you can't or don't want to smoke. Support will be available from your local smoking cessation programme, advice, or support will be available from Nicorette Cools Lozenge.

When using a quit attempt, behavioral therapy, advice and support will be available from your local smoking cessation programme, advice, or support will be available from Nicorette Cools Lozenge.

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dissolves to relieve cravings and nicotine withdrawal symptoms

lozenge
icy mint

nicorette® cools
2mg lozenge
nicotine

1x20 lozenges

2mg for smokers of 20 cigarettes or less a day
SAMPLE PACK
NOT FOR RESALE

Nicorette Cools
2 mg lozenge
nicotine

1 x 20
lozenges

2 mg
for smokers of
20 cigarettes
or less a day

dissolves to relieve cravings and nicotine withdrawal symptoms
TO OPEN
push and hold side to release and lift lid

TO CLOSE
click lid down
UKPAR Nicorette Cools 2 mg and 4 mg Lozenge

nicorette

Use: This product strength is suitable for those smoking 20 or less cigarettes a day. Nicorette 2mg lozenges are used to reinstate 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, Nicorette 2mg lozenges can be used in a number of ways, either to completely replace all your cigarettes, or if you do not feel ready to stop smoking completely, to replace certain cigarettes and therefore help you cut down the number of cigarettes you smoke. It may also help increase your motivation to quit.

Directions: For adults and children aged 12 years and over. Do not chew or swallow the lozenge. Place the lozenge in your mouth, and allow to dissolve. Use 1 lozenge when required, usually 6-12 lozenges per day. Do not use more than 15 lozenges per day. Read the enclosed leaflet carefully before use.

Warnings: Do not exceed the stated dose.

If you are pregnant, talk to your doctor, pharmacist or nurse before using this product. If you need any advice before starting to use this product, talk to your doctor, pharmacist or nurse.

Do not use if you are allergic to any of the ingredients listed below.

You are more likely to quit smoking when using this product with help from your pharmacist, doctor, a trained counsellor or a support programme.

Contents: The pack contains 20 compressed lozenges, each containing 2mg nicotine. Other ingredients are E421, E415, E605, E100, E901, E171, xanthan gum, sodium carbonate anhydrous, hypromellose, sorbitol, glycerol, polysorbate 60.

Storage: Keep out of the reach and sight of children.

Disposal of waste: Please read the enclosed leaflet for instructions.
nicorette®
cools 2 mg lozenge
nicotine

Use: This product strength is suitable for those smoking 20 or less cigarettes a day. Nicorette cools 2mg lozenge is used to relieve and/or prevent withdrawal symptoms and reduce the craving you get when you try to stop smoking or when cutting down the number of cigarettes you smoke. It provides a safer alternative to smoking for both the individual and those around them.

Ideally you should aim to stop smoking. However, Nicorette cools 2mg lozenge can be used in a number of ways, either to completely replace all your cigarettes, or if you do not feel ready to stop smoking completely, to replace certain cigarettes and therefore help you cut down the number of cigarettes you smoke. It may also help increase your motivation to quit.

Directions: For adults and children aged 12 years and over. Do not chew or swallow the lozenge. Place the lozenge in your mouth and allow to dissolve. Use 1 lozenge when required, usually 6-12 lozenges per day. Do not use more than 18 lozenges per day. Read the information leaflet carefully before use.

Warning: Do not exceed the stated dose.

If you are pregnant, talk to your doctor, pharmacist or nurse before using this product. If you need any advice before starting to use this product, talk to your doctor, pharmacist or nurse.

Do not use if you are allergic to any of the ingredients listed below.

You are more likely to quit smoking when using this product with help from your pharmacist, doctor, a trained counsellor or a support programme.

Contents: The pack contains 20 compressed lozenges, each containing 2mg nicotine. Other ingredients are E421, E415, E555, E950, E470c, E171, wintergreen flavour, sodium carbonate anhydrous, hypromellose, sepi film gloss, polysorbate 80.

Storage: Keep out of the reach and sight of children.

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

PL holder: McNeil Products Ltd
Maidenhead, Berkshire, SL6 3UK, UK

Batch No: 770023

Use before:

36
UKPAR Nicorette Cools 2 mg and 4 mg Lozenge

dissolves to relieve cravings and nicotine withdrawal symptoms

4 x 20 lozenges

2 mg

for smokers of 20 cigarettes or less a day

770024
nicorette
cools 2 mg

Use: This product strength is suitable for those smoking 20 or less cigarettes a day. Nicorette cools 2 mg lozenge is used to help you stop smoking or prevent withdrawal symptoms and reduce the craving you get when you try to stop smoking or when cutting down the number of cigarettes you smoke. It provides a safer alternative to smoking for both the individual and those around them.

Ideally you should aim to stop smoking. However, Nicorette cools 2 mg lozenge can be used in a number of ways, either to completely replace all your cigarettes, or if you do not feel ready to stop smoking completely, to replace certain cigarettes and therefore help you cut down the number of cigarettes you smoke. It may also help increase your motivation to quit.

Directions: For adults and children aged 12 years and over. Do not chew or swallow the lozenges. Place the lozenges in your mouth and allow to dissolve. Use 1 lozenge when required, usually 8-12 lozenges per day. Do not use more than 15 lozenges per day. Read the information leaflet carefully before use.

Warning: Do not exceed the stated dose.

If you are pregnant, talk to your doctor, pharmacist or nurse before using this product. If you need any advice before starting to use this product, talk to your doctor, pharmacist or nurse.

Do not use if you are allergic to any of the ingredients listed below.

You are more likely to quit smoking when using this product with help from your pharmacist, doctor, a trained counsellor or a support programme.

Contents: The pack contains 4 x 20 compressed lozenges, each containing 2 mg nicotine. Other ingredients are E421, E415, E963, E551, E470b, E171, winterfresh flavour, sodium carbonate anhydrous, hypromellose, sephadex glose, polysorbate 60.

Storage: Keep out of the reach and sight of children.

Dispose of sensibly. Please read the enclosed leaflet for instructions.
Nicorette Cools 2 mg and 4 mg Lozenge

nicorette®
cools 2 mg lozenge
nicotine

Use: This product strength is suitable for those smoking 20 or less cigarettes a day. Nicorette cools 2mg lozenge is used to relieve and 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, Nicorette cools 2mg lozenge can be used in a number of ways, either to completely replace all your cigarettes, or if you do not feel ready to stop smoking completely, to replace certain cigarettes and therefore help you cut down the number of cigarettes you smoke. It may also help increase your motivation to quit.

Directions: For adults and children aged 12 years and over. Do not chew or swallow the lozenges. Place the lozenge in your mouth and allow to dissolve. Use 1 lozenge when required, usually 5-12 lozenges per day. Do not use more than 15 lozenges per day. Read the information leaflet carefully before use.

Warnings: Do not exceed the stated dose.

If you are pregnant, talk to your doctor, pharmacist or nurse before using this product. If you need any advice before starting to use this product, talk to your doctor, pharmacist or nurse.

Do not use if you are allergic to any of the ingredients listed below.

You are more likely to quit smoking when using this product with help from your pharmacist, doctor, a trained counsellor or a support programme.

Contents: The pack contains 4x20 compressed lozenges, each containing 2mg nicotine. Other ingredients are E421, E415, E965, E330, E706, E171, winterfresh flavour, sodium carbonate anhydrous, hypromellose, eepifilm gloss, polyalkene glycol 80.

Storage: Keep out of the reach and sight of children.

Dispose of safely. 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

Batch No: 770025

Use before:
TO OPEN
push and hold slide to release and lift lid

TO CLOSE
click lid down
nicorette® cools 2mg

1 lozenge contains 2 mg nicotine (as nicotine resinate).
Do not use more than 15 lozenges/day.
To be dissolved in the mouth. Do not chew or swallow the lozenge.
Read the package leaflet before use.
Keep out of reach and sight of children.

Pl. Holder: McNeil Products Ltd
Maidenhead, Berkshire, SL6 8UG, UK
dissolves to relieve cravings and nicotine withdrawal symptoms

nicorette cools 4mg lozenge nicotine

4×20 lozenges

for smokers of more than 20 cigarettes a day
Use: This product strength is suitable for those others who need to stop smoking 30 cigarettes a day, who smoke up to 2 mg of nicotine per day. Nicorette lozenges are a useful aid to help you cut down the number of cigarettes you smoke, and it may also help increase your motivation to quit. Ideally you should aim to stop smoking. However, Nicorette lozenges can be used in a number of ways, to either completely replace all your cigarettes, or if you do not feel ready to stop smoking completely, to replace certain cigarettes and therefore help you cut down the number of cigarettes you smoke. It may also help increase your motivation to quit.

Directions: For adults and children aged 12 years and over, put one lozenge in your mouth and allow it to dissolve. Use 1 lozenge when required, not more than 12 lozenges per day. Do not use more than 15 lozenges per day. Read the information leaflet carefully before use.

Warning: Do not exceed the stated dose.

If you are pregnant, talk to your doctor, pharmacist or nurse before using this product. If you need any advice before starting to use this product, talk to your doctor, pharmacist or nurse.

You are more likely to quit smoking when using this product with help from your doctor, pharmacist, or a support group.

Contents: The pack contains 4020 lozenge sachets, each containing 4 mg nicotine. Other ingredients are: E402, E415, E550, E555, E470c, E171, water-soluble sodium carbonate syrups, hypromellose, cellulose, glycerol, propylene GL.

Storage: Keep out of the reach and sight of children.

Dispose of safely. Please read the enclosed leaflet for instructions.
nicorette®
cools 4 mg lozenge
nicotine

Use: This product strength is suitable for those smoking more than 20 cigarettes a day. Nicorette cools 4 mg lozenge is used to relieve and or prevent withdrawal symptoms and to 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.
Ideal for those who want to stop smoking. However, Nicorette cools 4 mg lozenge can be used in a number of ways, either to completely replace all your cigarettes, or if you do not feel ready to stop smoking completely, to replace certain cigarettes and therefore help you cut down the number of cigarettes you smoke. It may also help increase your motivation to quit.

Directions: For adults and children aged 12 years and over. Do not chew or swallow the lozenges. Place the lozenge in your mouth and allow to dissolve. Use 1 lozenge when required, usually 9-12 lozenges per day. Do not use more than 15 lozenges per day. Read the information leaflet carefully before use.

Warning: Do not exceed the stated dose.

If you are pregnant, talk to your doctor, pharmacist or nurse before using this product. If you need any advice before starting to use this product, talk to your doctor, pharmacist or nurse.
Do not use if you are allergic to any of the ingredients listed below.
You are more likely to quit smoking when using this product with help from your pharmacist, doctor, a trained counsellor or a support programme.

Contents: The pack contains 4x20 compressed lozenges, each containing 4 mg nicotine. Other ingredients are E421, E415, E655, E600, E471e, E171, winterfresh flavour, sodium carbonate anhydrous, hypromellose, sepilin glue, polysorbate 80.

Storage: Keep out of the reach and sight of children. Disposing 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
PL holder: McNeil Products Ltd
Mardenhead, Berkashi, SL8 5UG, UK
PL 15513/0375

Batch No: 770029
Use before:
1 lozenge contains 4 mg nicotine (as nicotine resinate).
Do not use more than 15 lozenges/day.
To be dissolved in the mouth. Do not chew or swallow the lozenge.
Read the package leaflet before use.
Keep out of reach and sight of children.

PL Holder: McNeil Products Ltd
Maidenhead, Berkshire, SL6 3UG, UK