

Public Assessment Report

Nicorette Microtab Lemon 2mg sublingual tablets

Nicotine bitartrate dihydrate

PL 15513/0156

McNeil Products Ltd

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Lay Summary

The MHRA granted McNeil Products Ltd a Marketing Authorisation (licence) for the medicinal product Nicorette Microtab Lemon 2mg Sublingual Tablets on 30/06/2009. The product is available without a medical prescription.

The product contains the active ingredient nicotine bitartrate dihydrate and is indicated for use in smoking reduction and cessation as replacement therapy. Nicotine replacement therapy is well known, and in the case of a generic product containing a widely used, well known active substance, no further clinical trials are required.

Scientific Discussion

INTRODUCTION

Based on a review of the data on quality, safety and efficacy, the UK granted a Marketing Authorisation for the medicinal product Nicorette Microtab Lemon 2mg Sublingual Tablets (PL 15513/0156) to McNeil Products Ltd on 30/06/2009. The product is available without a medical prescription.

This application was a national complex abridged application for sublingual tablets containing 2 mg Nicotine in the form of nicotine bitartrate dihydrate. This application was made under Article 8(3) of Directive 2001/83/EC, as amended. The application is a line extension to Nicorette 2mg Gum (PL 15513/0169) also held by McNeil Products Ltd.

The product contains the active ingredient nicotine bitartrate and is indicated for use in smoking reduction and cessation as replacement therapy. Nicotine replacement therapy is well known, and in the case of a line extension to an existing product containing a widely used, well known active substance, no further clinical trials are required and none are provided by the applicant.

A satisfactory bioequivalence study demonstrated the bioequivalence of the product with Nicorette 2mg Gum (PL 15513/0169).

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nicotine Bitartrate

USAN : Nicotine Bitartrate

Chemical names:

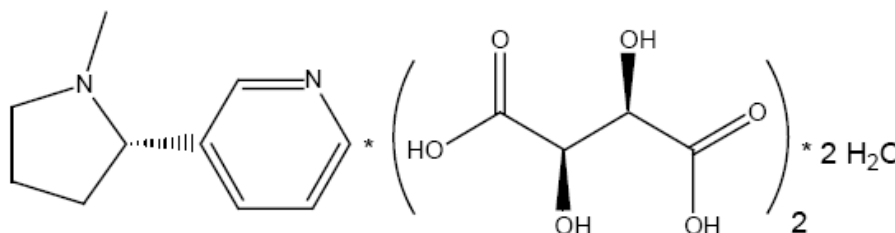
a) – Pyridine, 3-[(2S)-1-methyl-2-pyrrolidinyl]-, (2R,3R)-2,3-dihydroxybutanedioate (1:2), dihydrate

b) – Nicotine L-(+)-tartrate (1:2), dihydrate

Company code – 183788

CAS No. – 65-31-6 Nicotine bitartrate (anhydrous)
54-11-5 Nicotine (base)

Structural formula:



Molecular Formula: $C_{10}H_{14}N_2 \cdot 2C_4H_6O_6 \cdot 2H_2O$

MW: 498.4

General Properties: Nicotine bitartrate dihydrate is a white to off-white powder with a melting point of about 90°C.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

The active substance is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated to support the retest period.

DRUG PRODUCT

Other Ingredients

The other ingredients of the drug product are

Mannitol (E421)
Microcrystalline cellulose
Povidone
Methylcellulose
Silicified microcrystalline cellulose
Magnesium stearate
Lemon flavour
Aspartame (E951)
Flavour

Appropriate justification for the inclusion of each excipient has been provided. All the excipients comply with the relevant Ph Eur monographs with the exception of silicified microcrystalline cellulose, lemon flavour and flavour. These three excipients are tested to in-house specifications. Copies of in-house specifications for the three excipients have been provided. Satisfactory certificates of analysis have been provided for all excipients. The applicant has stated that no excipients of animal or human origin are used in the manufacture of the product.

Dissolution and impurity profiles

Dissolution and impurity profiles for the drug product were found to be similar to those for the reference products.

Manufacture

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Satisfactory process validation has been carried.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The sublingual tablets are to be packed into tear through polyamide/aluminium/PVC blisters sealed with a paper/PET/aluminium backing. A drawing of the blister and data sheet confirming the dimensions of the material has been provided. The container closure system has been demonstrated to meet current requirements.

Stability

Satisfactory stability studies have been conducted according to current requirements and support a shelf-life of 36 months with the following storage condition, “Do not store above 25°C”.

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation was granted.

PRE-CLINICAL ASSESSMENT

No pre-clinical data were provided and none were required for this abridged application.

MEDICAL ASSESSMENT

Clinical Pharmacology

The pharmacological effects of nicotine are well documented. Those resulting from using Nicorette Microtab Lemon are comparatively small. The response at any one time represents a summation of stimulant and depression actions from direct, reflex and chemical mediator influences on several organs. The principal pharmacological actions are central stimulation and/or depression; transient hyperpnoea; peripheral vasoconstriction (usually associated with a rise in systolic pressure); suppression of appetite and stimulation of peristalsis.

Pharmacokinetics

The amount of nicotine absorbed from a nicotine sublingual tablet depends on the amount of nicotine released in the oral cavity and the amount thereof that is swallowed. Most of the absorption of nicotine from Nicorette Microtab Lemon occurs directly through the buccal mucosa. The absolute bioavailability, after sublingual administration of the tablet, is approximately 50%. The systemic bioavailability of swallowed nicotine is lower due to the amount removed initially by the liver (the first-pass effect). Hence, the high and rapidly rising nicotine concentrations seen after smoking are rarely produced by treatment with nicotine sublingual tablets.

Steady-state trough nicotine plasma concentrations, achieved after ten hourly doses of one tablet, are in the order of magnitude of 10 ng/mL, which is about 50% of normal smoking levels.

Bioequivalence

To support the application, the applicant submitted two bioavailability studies: a single centre, single-blind, single dose, cross-over design trial; and a single centre, single blind, multiple dose, cross-over design trial respectively.

Study 1: Study No: 468-CHC-9125-003

Randomised, two-period, single dose, cross-over, bioequivalence study comparing the test 4mg Nicorette Microtab sublingual tablet (Pfizer) versus reference Nicorette Microtab 2 x 2mg sublingual tablet in healthy smokers.

Study protocol

24 healthy >10/day smokers, 12 male and 12 female, aged 21-50 years, were included in this study. One subject was withdrawn from the study. Each subject received a 4mg nicotine dose of one of two nicotine formulations. A randomisation scheme was included in the report. The following formulations were administered:

Reference: Nicorette Microtab 2 x 2mg (Pharmacia, Sweden. Batch No: CK812B)

Test : Nicorette Sublingual Tablet 4mg (Pfizer, Batch No: DAT 1109)

The reference is registered in UK. The tablets were given following a controlled period of fasting. Subjects were free to drink additional supplied non citrus fluids and eat from 2 h post-dose. Blood samples were taken at pre-dose and at 5, 10, 15, 20, 30, 45mins and 1, 1.25, 1.5, 2, 3, 4, 6, 8 and 10 hours after administration of the products.

Plasma samples were analysed for nicotine by LC-MS/MS by the laboratories of Pharmacia AB, Helsingborg, Sweden. The limit of quantitation was 0.1ng/ml. The method was validated and the validation report was provided.

$AUC_{(0-t)}$, $AUC_{(0-inf)}$, C_{max} , t_{max} and $t_{1/2}$ were calculated according normal standard procedures.

Statistical evaluation was performed for $AUC_{(0-t)}$, AUC_{inf} and C_{max} with ANOVA and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated.

Difference treatment A and B
Dose corrected data

Parameter	Number of subjects	Ratio (%)	Lower limit (%)	Upper limit (%)
AUCinf	23	97.60	90	106
Cmax	23	100.50	90	112
AUClast	23	99.56	91	109

Study 2: Study No: 468-CHC-9125-003

Study protocol

24 healthy >10/day smokers, 12 male and 12 female, aged 21-50 years, were included in this study. Each subject received a 2mg nicotine dose of one of three nicotine formulations: Nicorette test sublingual tablet; Nicorette test S/L tablet used as a lozenge; and a Nicotine 2mg Gum.

For each subject there was a 2mg dose hourly for 11 hours, a total of 12 doses. A randomisation scheme was included in the report. The following formulations were administered:

Treatment A: Nicorette test Sublingual tablet

Treatment B: Nicorette test S/L tablet used as a lozenge

Treatment D: Nicorette Gum

The tablets were given following breakfast and no intake of nicotine for >12hours. Subjects were free to drink additional supplied non citrus fluids. Blood samples were taken at pre-dose and at 10, 20, 30, 40, 50 and 60mins after administration of the products.

Statistical evaluation was performed for $AUC_{(0-t)}$, AUC_{inf} and C_{max} with ANOVA and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated

Bioequivalence treatment A vs. D

Parameter	Number of subjects	Arithmetic mean	Ratio of means	Geometric mean	Intersubject variance	Intrasubject variance	Lower CL	Upper CL
Cmax	24	0.95	1.07	0.99	0.137	0.065	0.871	1.124
AUC11-12	24	1.07	1.09	1.00	0.140	0.064	0.885	1.140

Bioequivalence treatment A vs. D, dose corrected.

Parameter	Number of subjects	Arithmetic mean	Ratio of means	Geometric mean	Intersubject variance	Intrasubject variance	Lower CL	Upper CL
Cmax	24	1.57	1.13	1.04	0.137	0.065	0.915	1.180
AUC11-12	24	1.63	1.15	1.05	0.140	0.064	0.930	1.197

Bioequivalence treatment B vs. D

Parameter	Number of subjects	Arithmetic mean	Ratio of means	Geometric mean	Intersubject variance	Intrasubject variance	Lower CL	Upper CL
Cmax	24	-0.02	1.00	0.94	0.141	0.040	0.850	1.038
AUC11-12	24	0.18	1.01	0.95	0.142	0.043	0.859	1.055

Bioequivalence treatment B vs. D, dose corrected.

Parameter	Number of subjects	Arithmetic mean	Ratio of means	Geometric mean	Intersubject variance	Intrasubject variance	Lower CL	Upper CL
Cmax	24	0.59	1.05	0.99	0.141	0.040	0.893	1.090
AUC11-12	24	0.74	1.07	1.00	0.142	0.043	0.902	1.108

Bioequivalence of the 2mg microtab to the reference 2mg Gum was demonstrated.

EFFICACY

No new data are submitted and none are required for this type of application.

SAFETY

No new data are submitted and none are required for this type of application.

EXPERT REPORTS

A satisfactory expert report is provided by an appropriately qualified individual.

PATIENT INFORMATION LEAFLET (PIL)

The PIL was assessed and is now acceptable.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC was assessed and is now acceptable.

LABELLING

The labelling was assessed and is now acceptable.

CONCLUSION

A Market Authorisation may be granted.

Overall Conclusion and Risk/Benefit Analysis

Quality

The important quality characteristics of Nicorette Microtab 2mg Lemon Sublingual Tablets 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.

Pre-Clinical

No new preclinical data were submitted and none are required for applications of this type.

Clinical

Bioequivalence has been demonstrated between the applicant's Nicorette Microtab 2mg Lemon Sublingual Tablets and Nicorette 2mg Gum (PL 15513/0169). No new or unexpected safety concerns arise from these applications. The SPC, PIL and labelling are satisfactory.

Risk/Benefit Analysis

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with nicotine bitartrate dihydrate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Steps Taken During Assessment

1	The MHRA received the application on 07/03/2006.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 15/03/2006.
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 17/01/2007, 08/01/2009 and 07/052009.
4	The applicant provided further information in regard to the quality assessment on 24/05/2007, 05/02/2008, 08/08/2008, 08/01/2009, 07/05/2009, and 05/06/2009.
5	The application was determined on 30/06/2009.

Steps Taken after Assessment

No non-confidential changes have been made to the market authorisation.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nicorette Microtab Lemon 2 mg sublingual tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nicotine bitartrate equivalent to 2.0 mg nicotine per tablet.

Nicotine Microtab Lemon also contains the ingredient aspartame. Please see section 4.4.

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Sublingual tablet.

White to off-white flat round, bevel-edged tablets engraved on one side with 'N2'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nicorette Microtab Lemon is indicated for the relief of nicotine withdrawal symptoms as an aid to smoking cessation in adults and children over 12 years of age. It is also indicated in pregnant and lactating women (see section 4.6).

In smokers currently unable or not ready to stop smoking abruptly, Nicorette Microtab Lemon may also be used as part of a programme to reduce smoking prior to stopping completely.

If possible, Nicorette Microtab Lemon should be used in conjunction with a behavioural support programme.

4.2 Posology and method of administration

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

Smoking cessation

Adults (over 18 years of age)

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

The initial dose is based on the individual's nicotine dependence. The tablet is used sublingually with a recommended dose of one tablet per hour or, for heavy smokers (smoking more than 20 cigarettes per day), two tablets per hour. Increasing to two tablets per hour may be considered for patients who fail to stop smoking with the one tablet-per-hour regimen or for those whose nicotine withdrawal symptoms remain so strong as to foresee a relapse.

Most smokers require 8 to 12 or 16 to 24 tablets per day, not to exceed 40 tablets. The duration of treatment depends on the individual, but up to three months of treatment is recommended. The nicotine dose should then be gradually reduced, by decreasing the total number of tablets used per day. The treatment should be stopped when the daily consumption is down to one or two tablets.

Adults who use nicotine replacement therapy (NRT) beyond 9 months are recommended to seek additional help and advice from a healthcare professional.

Adolescents (12 to 18 years)

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

The initial dose is based on the individual's nicotine dependence. The tablet is used sublingually with a recommended dose of one tablet per hour or, for heavy smokers (smoking more than 20 cigarettes per day), two tablets per hour. Increasing to two tablets per hour may be considered for patients who fail to stop smoking with the one tablet-per-hour regimen or for those whose nicotine withdrawal symptoms remain so strong as to foresee a relapse.

Most smokers require 8 to 12 or 16 to 24 tablets per day, not to exceed 40 tablets. Use for up to 8 weeks to break the habit of smoking, then gradually

reduce the dose over a 4 week period. The treatment should be stopped when the daily consumption is down to one or two tablets. As data are limited in this age group, the recommended duration of treatment is 12 weeks. If longer treatment is required, advice from a healthcare professional should be sought.

Children (under 12 years)

There is no relevant indication for the use of Nicorette Microtab Lemon in children under 12.

Smoking reduction

Adults (over 18 years of age)

Use Nicorette Microtab Lemon between smoking episodes to manage the urge to smoke, to prolong smoke-free intervals and with the intention to reduce smoking as much as possible. If a reduction in number of cigarettes per day has not been achieved after 6 weeks, professional advice should be sought.

A quit attempt should be made as soon as the smoker feels ready, but not later than 6 months after start of treatment. If a quit attempt cannot be made within 9 months after starting treatment, professional advice should be sought.

When making a quit attempt the smoking cessation instructions above can be followed.

Adolescents (12 to 18 years)

Where adolescents are motivated to stop smoking abruptly, smoking cessation should be recommended. However, smoking reduction can be considered where adolescents are not ready or able to stop smoking abruptly. As data are limited in this age group, and the recommended duration of NRT is 12 weeks, adolescents should consult a healthcare professional before starting the “smoking reduction prior to stopping” regimen.

Use Nicorette Microtab Lemon between smoking episodes to manage the urge to smoke, to prolong smoke-free intervals and with the intention to reduce smoking as much as possible. If a reduction in number of cigarettes per day has not been achieved after 6 weeks, professional advice should be sought.

A quit attempt should be made as soon as the smoker feels ready, but not later than 6 months after start of treatment. If a quit attempt cannot be made within 9 months after starting treatment, professional advice should be sought.

When making a quit attempt the smoking cessation instructions for adolescents (12 to 18 years) given above can be followed.

Children (under 12 years)

There is no relevant indication for the use of Nicorette Microtab Lemon in children under 12.

4.3 Contraindications

Hypersensitivity to nicotine or any other component of the sublingual tablet.

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.

Nicorette Microtab Lemon contains the ingredient aspartame which is a source of phenylalanine and may be harmful for people with phenylketonuria.

Underlying cardiovascular disease: In stable cardiovascular disease Nicorette Microtab Lemon presents a lesser hazard than continuing to smoke. However dependent smokers currently hospitalised as a result of myocardial infarction, severe dysrhythmia or CVA and who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions. If this fails, Nicorette Microtab 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.

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. Ulcerative stomatitis has been reported.

Renal or hepatic impairment: Nicorette Microtab Lemon 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.

Phaeochromocytoma and uncontrolled hyperthyroidism: As nicotine causes release of catecholamines, Nicorette Microtab Lemon 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: See section 4.5

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.

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.

4.6 Pregnancy and lactation

Pregnancy

NRT is not contraindicated in pregnancy. The decision to use NRT should be made on a risk-benefit assessment as early on in the pregnancy as possible with the aim of discontinuing use as soon as possible.

Smoking during pregnancy is associated with risks such as intra-uterine growth retardation, premature birth or stillbirth. Stopping smoking is the single most effective intervention for improving the health of both pregnant smoker and her baby. The earlier abstinence is achieved the better.

Ideally smoking cessation during pregnancy should be achieved without NRT. However for women unable to quit on their own, NRT may be recommended to assist a quit attempt.

Nicotine passes to the foetus affecting breathing movements and has a dose-dependent effect on placental/foetal circulation. However the risk of using NRT to the foetus is lower than that expected with tobacco smoking, due to lower maximal plasma nicotine concentration and no additional exposure to polycyclic hydrocarbons and carbon monoxide.

Intermittent dosing products may be preferable as these usually provide a lower daily dose of nicotine than patches. However, patches may be preferred

if the woman is suffering from nausea during pregnancy. If patches are used they should be removed before going to bed.

Lactation

NRT is not contraindicated in lactation. Nicotine from smoking and NRT is found in breast milk. However the amount of nicotine the infant is exposed to is relatively small and less hazardous than the second-hand smoke they would otherwise be exposed.

Using intermittent dose NRT preparations, compared with patches, may minimize the amount of nicotine in the breast milk as the time between administrations of NRT and feeding can be more easily prolonged.

4.7 Effects on ability to drive and use machines

This medicinal product 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; irritability/aggression, dysphoria/depressed mood, anxiety, restlessness, poor concentration, increased appetite/weight gain, urges to smoke (cravings), night-time awakenings/sleep disturbance and decreased heart rate.

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

Nicorette Microtab Lemon 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 Microtab Lemon has not been found to cause any serious adverse effects. Excessive consumption of Nicorette Microtab Lemon by those who have not been in the habit of inhaling tobacco smoke could possibly lead to nausea, faintness or headaches.

Most of the undesirable effects associated with Nicorette Microtab Lemon occur during the first 3-4 weeks after starting treatment.

Reported adverse events associated with Nicorette Microtab Lemon include:

Body System	Incidence*	Reported adverse event
Nervous system disorders:	Common:	Dizziness, headache
Cardiac disorders:	Common:	Palpitations
	Very rare:	Reversible atrial fibrillation
Respiratory, thoracic and mediastinal disorders:	Common:	Coughing
Gastrointestinal disorders:	Common:	Gastrointestinal discomfort, hiccups, nausea
General disorders and administration site disorders:	Common:	Sore mouth or throat, dry mouth, burning sensation in the mouth, rhinitis
	Rare:	Allergic reactions including angioedema

* 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), including isolated reports.

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, 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 for treatment of addiction

ATC code: N07B A01

The pharmacological effects of nicotine are well documented. Those resulting from using Nicorette Microtab Lemon are comparatively small. The response at any one time represents a summation of stimulant and depression actions from direct, reflex and chemical mediator influences on several organs. The principal pharmacological actions are central stimulation and/or depression; transient hyperpnoea; peripheral vasoconstriction (usually associated with a rise in systolic pressure); suppression of appetite and stimulation of peristalsis.

5.2 Pharmacokinetic properties

The amount of nicotine absorbed from a nicotine sublingual tablet depends on the amount of nicotine released in the oral cavity and the amount thereof that is swallowed. Most of the absorption of nicotine from Nicorette Microtab Lemon occurs directly through the buccal mucosa. The absolute bioavailability, after sublingual administration of the tablet, is approximately 50%. The systemic bioavailability of swallowed nicotine is lower due to the amount removed initially by the liver (the first-pass effect). Hence, the high and rapidly rising nicotine concentrations seen after smoking are rarely produced by treatment with nicotine sublingual tablets.

Steady-state trough nicotine plasma concentrations, achieved after ten hourly doses of one tablet, are in the order of magnitude of 10 ng/mL, which is about 50% of normal smoking levels.

There is a slight deviation from dose-linearity of AUC_{inf} and C_{max} when single doses of one, two and three tablets are given. This deviation may be explained by a larger fraction of the higher doses being swallowed and subject to first-pass elimination.

The volume of distribution following i.v. 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 significant effects on nicotine kinetics.

The major eliminating organ is the liver, and average plasma clearance is about 70 l/hour and the half-life approximately 2 hours. 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.

The primary urinary metabolites are cotinine (15% of the dose) and trans-3-hydroxy-cotinine (45% 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.

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 patients undergoing haemodialysis.

Hepatic impairment

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

5.3 Preclinical safety data

Preclinical data indicate that nicotine is neither mutagenic or genotoxic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Microcrystalline cellulose
Povidone
Methylcellulose
Silicified microcrystalline cellulose
Magnesium stearate
Lemon flavour
Aspartame (E951)
Flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Pack sizes

Cardboard box of 30 and 100 sublingual tablets with a package insert/booklet.

AL/AL blister strips of 10 sublingual tablets.

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 15513/0156

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

30/06/2009

10 DATE OF REVISION OF THE TEXT

30/06/2009

Labels and Leaflets



nicorette[®]
**microtab
 lemon 2 mg**
**nicotine
 sublingual tablet**
 with

A guide for users

What you should know about nicorette[®] microtab lemon 2 mg (2 mg nicotine sublingual tablets)

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.

In this leaflet

- 1 What this medicine is for [page 4](#)
- 2 Before using this medicine [page 6](#)
 - Do not use Nicorette Microtab Lemon [page 6](#)
 - Talk to your doctor, nurse or pharmacist [page 6](#)

- If you are pregnant or breast-feeding [page 8](#)
- 3 How and when to use this medicine [page 10](#)
 - How to use Nicorette Microtab Lemon [page 10](#)
 - When to use Nicorette Microtab Lemon [page 11](#)
 - How to stop smoking your choice [page 13](#)
 - Stopping Immediately [page 15](#)
 - Adults aged 18 years and over
 - Children aged 12 years and over
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1 What this medicine is for

Nicorette microtab lemon 2 mg is a nicotine replacement therapy (NRT). It is used to relieve withdrawal symptoms and reduce the cravings for nicotine that you get when you try to stop smoking or when you are cutting down the number of cigarettes you smoke while trying to stop smoking. This product will help relieve your cravings. To help cut down or quit smoking you should also try to use a behavioural support programme to increase your chances of success. Details of Nicorette ActiveStop are shown in Section 8 of this booklet.

IMPORTANT: Nicorette microtab lemon 2 mg is a sublingual tablet which means it must be dissolved under the tongue and NOT swallowed or chewed.

What does Nicorette Microtab Lemon 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 microtab lemon 2 mg, nicotine is released and passes into your body through the lining of your mouth. The nicotine released is sufficient to relieve the unpleasant nicotine withdrawal symptoms. It will also help to stop your craving to smoke but will not give you the "buzz" you get from smoking a cigarette.

The benefits of stopping smoking far outweigh any potential risk from using nicotine from NRT. It is the toxins in cigarette smoke such as tar, lead, cyanide and ammonia that cause smoking related

disease and death, not the nicotine.

2 Before using this medicine

- **Do not use Nicorette Microtab Lemon:**
 - if you have an allergy to nicotine or any of the other ingredients.
- ▲ **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 page 8 *If you are pregnant or breast-feeding*

- if you are in hospital because of heart disease (including heart attack, disorders of heart rate or rhythm, or stroke)
 - In other heart conditions not requiring you to be in hospital, using NRT is better than continuing to smoke
- if you have phenylketonuria which is a rare hereditary condition
- 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 pheochromocytoma (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 microtab lemon 2 mg as you may find your insulin or medication requirements alter

- If you are taking other medicines such as theophylline, doxapine or ropinirole. Stopping smoking or cutting down may require the dose of these medicines to be adjusted.
- If any of these applies, talk to your doctor, nurse or pharmacist.

⚠ Some of the ingredients can cause problems

- This product contains aspartame, which is a source of phenylalanine. This may be harmful if you have a condition called "phenylketonuria".

⚠ If you are pregnant or breast-feeding

If you are pregnant, ideally, you should try to give up smoking without NRT. If

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you can't manage this, you can use NRT 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 microtab lemon 2 mg, 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, ideally, you should try to give up smoking without NRT. 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 microtab lemon 2 mg to make sure that the baby gets the smallest amount of nicotine possible.

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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

1 How to use Nicorette Microtab Lemon

Place the microtab under your tongue. Allow it to slowly dissolve. This will release nicotine, which you will absorb through the lining of your mouth. nicorette microtab lemon 2 mg should NOT be chewed or swallowed.

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1 When to use Nicorette Microtab Lemon

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

Please read the information carefully and then go to the "How to stop smoking: your choice" section on page 13, which will help you decide which method to use to give up smoking.

- The number of nicorette microtab lemon 2 mg you use each day will depend on how many cigarettes you smoked and how strong they were. See dosing information below to find out the dose you should take.

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1 Children under 12 years

Do not give this product to children under 12 years.

1 Adults and Children 12 years and over

Number of Cigarettes you smoke per day	Dose of Microtabs
20 cigarettes or fewer	One microtab to be taken every hour
More than 20 cigarettes	Two microtabs to be taken every hour

- Most people take between 8 to 24 microtabs per day.
- Do not take more than 40 per day.
- Children aged 12 and up to 18 years should not use for longer than 12 weeks in total without asking for help and advice from a doctor, nurse or pharmacist.

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- Adults aged 18 years and over should not use for more than 9 months in total without asking for help and advice from a doctor, nurse or pharmacist.

1 How to stop smoking : your choice

Because smoking is an addiction you may find it difficult to give up. From time to time you may still have strong urges to smoke but if you follow these recommendations, you have a good chance of quitting.

Some people may find it easier to set a date to quit and stop smoking immediately.

Others who are unable or not ready to stop smoking abruptly, may benefit from gradually reducing the number of cigarettes they smoke each day

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until they feel ready to stop completely.

If you are an adult you can follow either one of these options. However children should follow the guide to stopping immediately as the recommended duration of nicotine replacement therapy in children is 12 weeks maximum. The only time children should stop gradually is if they are having a problem stopping immediately and they should talk to their doctor, nurse or pharmacist beforehand.

If you find it hard to stop using nicorette microtab lemon 2 mg, you are worried that you will start smoking again without it or you find it difficult to reduce the number of tablets you are using, talk to your doctor, nurse or pharmacist.

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Remember nicorette microtab lemon 2 mg is not intended as a substitute for smoking, it is an aid to give up.

Use one of the two options which follow.

1 Stopping immediately

The idea is to stop smoking immediately and use the microtabs to relieve the cravings to smoke. After achieving this you then stop using the microtabs.

There is a difference in how you stop depending on whether you are aged between 12 - 18 years or 18 years and over. Make sure you follow the age range applicable to you.

1 Adults aged 18 years and over

See the following diagrams which show the basic step by step process. The time given in step 2 is the

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longest amount of time it should take, and you should try to achieve your move to the next step in the shortest time possible.
Make sure you read the instructions for each step in the information which follows.

Preparation	12 weeks (3 months)	Gradually reduce usage
Step 1	Step 2	Step 3

- Step 1:** Set a date to quit and stop smoking cigarettes.
- Step 2:** Use 1 or 2 microtabs every hour to relieve your cravings. See "Dosage" section on pages 12-13 to decide on the dose you should take.
 - Use Nicorette Microtab Lemon 2 mg for up to 12 weeks

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(3 months) to relieve your cravings to smoke.
Step 3: Start reducing the number of tablets you take each day. Once you reach only one or two tablets each day you should try to stop completely.

- If you need to use the microtabs for longer than a total of 9 months, ask your doctor, nurse or pharmacist for advice.
- You might feel a sudden craving to smoke long after you have given up smoking and stopped using the Nicorette Microtab Lemon 2 mg. Remember you can use nicotine replacement therapy again if this should happen.

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Children aged 12 years and over

See the following diagrams which show the basic step by step process. The time given in step 2 and 3 are the longest amount of time it should take, and you should try to achieve your move to the next step in the shortest amount of time. The total amount of time taken to stop smoking should not exceed 12 weeks. Make sure you read the instructions for each step in the information which follows.

Preparation	8 weeks (2 months)	4 weeks (1 month)
Step 1	Step 2	Step 3

- Step 1:** Set a date to quit and stop smoking cigarettes.
- Step 2:** Use 1 or 2 microtabs every hour to relieve your cravings.

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See "Dosage" section on pages 12-13 to decide on the dose you should take.

- Use the Nicorette Microtab Lemon 2 mg for up to 8 weeks (2 months) to relieve your cravings to smoke.
- Step 3:** Start reducing the number of tablets you take each day over the next 4 week period. Once you reach only one or two tablets each day you should try to stop completely. You should make sure that you do this within the 4 weeks.

- If you need to use the microtabs for longer than the 12 weeks (3 months), ask your doctor, nurse or pharmacist for advice.

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Stopping Gradually

The idea is to start gradually replacing some of your cigarettes with the microtabs. After achieving this you then give up cigarettes completely while using the microtabs. Finally you give up using the microtabs. There is a difference in how you stop depending on whether you are aged between 12-18 years or 18 years and over. Make sure you follow the age range applicable to you.

Adults aged 18 years and over

See the following diagram which shows the basic step by step process. The time given for step 2 is the longest it should take, and you should try to achieve your move to the next step in the shortest time possible. Make sure you read the instructions

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for each step in the information which follows.

Preparation	24 weeks (6 months)	12 weeks (2 months)	Gradually reduce usage
Step 1	Step 2	Step 2	Step 4

- Step 1:** Work out how many cigarettes you smoke per day. Set a date to start reducing the number of cigarettes you smoke.
- Step 2:** Start reducing. Over the next few months, reduce the number of cigarettes you smoke by using 1 or 2 microtabs every hour to relieve your cravings. See "Dosage" section on pages 12-13.

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- If after 6 weeks you have not reduced the number of cigarettes you smoke, ask your doctor, nurse or pharmacist for advice.
- You should aim to stop smoking completely by six months from the beginning of treatment.

- Step 3:** Stop smoking. Cut out all cigarettes and continue using the microtabs for 3 months to relieve your cravings to smoke.
- Step 4:** Start reducing the use of the microtabs. You should try to use fewer microtabs each day. When you are using only one or two microtabs per day you should stop completely.

- If you need to use the product for longer than 9 months, ask your doctor, nurse or pharmacist for advice.

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- You might feel a sudden craving to smoke long after you have given up smoking and stopped using Nicorette Microtab Lemon 2 mg. Remember you can use nicotine replacement therapy again if this should happen.

Children aged 12 years and over

Children should follow the guide to stopping immediately. The recommended duration of nicotine replacement therapy in children is 12 weeks maximum. The only time children should stop gradually is if they are having a problem stopping immediately. Talk to your doctor, nurse or pharmacist before attempting to stop gradually.

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▲ If you have used too many Nicorette Microtab Lemon

If you have used more than the recommended number of tablets you may experience nausea, 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 Microtab Lemon

- Contact a doctor or your nearest hospital Accident and Emergency department immediately if a child under 12 years uses, chews, sucks or

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swallows a nicorette microtab lemon 2 mg tablet. Take this leaflet and the pack with you.
Nicotine ingestion by a child may result in severe poisoning.

4 Possible side-effects

Like all medicines, nicorette microtab lemon 2mg 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

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nicotine you are taking. You may also experience these effects if you use too few nicorette microtab lemon 2 mg tablets before you are ready to reduce your nicotine intake.

▲ These effects include:

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

Effects of too much nicotine

You may also get these effects if you are not used to inhaling tobacco smoke.

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- dry mouth

Rare side-effects:

(less than 1 in 1,000 people are affected)

- Allergic reaction (swelling of the mouth, lips, throat and tongue, itching of the skin, swelling of the skin, ulceration and inflammation of the lining of the mouth)

Very rare side-effects:

(less than 1 in 10,000 people are affected)

- abnormal beating of the heart

► 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.

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▲ These effects include:

- feeling faint
- feeling sick (nausea)
- headache

Side-effects of Nicorette Microtab Lemon

Common side-effects:

(less than 1 in every 10 people are affected)

- headache
- dizziness
- chest palpitations
- cough
- stomach discomfort
- hiccups
- feeling sick (nausea)
- sore mouth or throat
- burning sensation in the mouth
- irritated nose (rhinitis)

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5 Storing and disposal

- Keep nicorette microtab lemon 2 mg out of the reach and sight of children. Nicotine in high doses can be very dangerous and sometimes fatal if taken by small children.

- Do not store nicorette microtab lemon 2 mg above 25°C.

- Do not use nicorette microtab lemon 2 mg after the 'Use before' date shown on the carton or blister. The expiry date refers to the last day of the month.

- Dispose of any unused nicorette microtab lemon 2mg sensibly and away from children. 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.

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6 Further information

What's in this medicine?

The active ingredient is: 2 mg nicotine. Other ingredients are: Mannitol (E421), microcrystalline cellulose, povidone, methylcellulose, silicified microcrystalline cellulose, magnesium stearate, lemon flavour, aspartame (E951), flavour.

What the medicine looks like

Nicorette microtab lemon 2 mg are blister packed in units of 10 microtabs, and is available in cartons containing 30 and 100 microtabs. Not all pack sizes may be marketed.

Who makes Nicorette Microtab Lemon?

The Product Licence holder is McNeil Products Ltd, Maidenhead, Berkshire, SL6 3UG, UK.

The manufacturer is McNeil AB, Helsingborg, Sweden.

This leaflet was revised in April 2009. ©

7 Helpful tips on giving up

You may have tried to stop smoking before and you know from bitter experience that it's not easy to give up cigarettes.

However, you have now taken the first constructive step towards becoming a non-smoker. In overcoming your tobacco dependence you will have to tackle two problems:

- 1 Your smoking habit.
- 2 Your addiction to nicotine.

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Willpower

The overriding success factor in quitting is how determined you are. The first few weeks of quitting will probably be the most difficult because your smoking ritual is still fresh in your mind.

However, you will find that as time goes by, your willpower becomes stronger. Telling friends, family and work colleagues that you have quit smoking and that you envisage a tough time ahead will encourage them to support you.

1 Pick the right day

There is never a perfect time to give up smoking, but you should plan ahead by choosing a date in the not too distant future on which you are going to give up cigarettes completely. This is your Quit Day. Try to pick a day when you will not be too stressed.

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2 Break your routine

For a number of years you will have become accustomed to smoking at certain times, with particular people or in certain situations. Think about the times you will miss smoking the most and plan how you will cope on these occasions. Changing your routine will help you break the habit of smoking.

3 Quit with a friend

Quitting with a fellow smoker is a good idea. It will strengthen your resolve and build on your determination.

Encourage a friend or family member to quit with you. It will give your morale a boost since there will be another person knowing exactly what you're feeling and with whom you can share your resolve to quit smoking.

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4 Remove any temptation

To help yourself succeed be sure to remove all cigarettes, matches, lighters etc. from your home, car and work. Ask your friends and colleagues not to offer you cigarettes or smoke dose by you but be careful not to offend them. Explain that you have given up. This type of support from friends is of greatest benefit for the first couple of weeks of quitting, as this is your most vulnerable time. The last thing you want is a cigarette close at hand in a moment of weakness.

5 Take one day at a time

When you reach your Quit Day, don't allow yourself to think that you're quitting for good. That will make it seem like a superhuman task. Just promise yourself "I won't have a

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cigarette today" and take it one day at a time. You'll be surprised how much that little thought helps.

6 Distract yourself

Whenever you feel the urge to smoke coming on, distract yourself by keeping active. Don't feel sorry for yourself. Get up and do something. Do that job around the house or garden that you've been putting off or take up a hobby.

Remember that the craving only lasts a few minutes.

7 Learn to relax

Once you have stopped smoking, taking exercise regularly will not only help you get fitter but will encourage you to relax. Exercise has the ability to relieve stress and tension. Taken

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regularly it will benefit you physically and psychologically.

If you haven't exercised for some time, take it slowly to begin with and increase the amount of time spent exercising over the course of a few weeks. Not only will exercising help you relax but it also helps to keep your weight under control, which some people find a problem when quitting.

8 Think cash not ash

One of the really noticeable benefits of 'stopping' is the extra cash that's suddenly available. To emphasize the point put the money into a pot marked 'cash not ash' and watch it accumulate. But be sure to use the money to treat yourself. You deserve a reward for not smoking.

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9 Dealing with relapses

You might find that in times of stress, reaching for a cigarette is the only thing that will help you through. There may also be certain situations – particularly social situations such as a party – where temptation just gets the better of you, so you smoke one or two cigarettes.

You might feel that your only option is to go back to smoking. Don't think of it as having failed, just think through the reasons why you wanted to quit in the first place and don't let those couple of cigarettes get the better of you. Refer back to your plan and start again. You can beat it!

10 If you don't succeed

Giving up is more difficult for some people than others. If you fail to stop first time, don't be

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disheartened. Try again at a later date – you can do it! Remember the most successful long term ex-smokers have usually had to try several times to stop smoking – if you don't succeed – quit quit again.

For further information

Read about Nicorette ActiveStop on the next page. This is a personalised mobile phone and online support programme which works with Nicorette to support you, body and mind, with the aim of helping you give up smoking.

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8 Nicorette ActiveStop



Personalised mobile phone and online support programme

Call now on 0800 244 838.

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How can ActiveStop help me?

- ▶ Nicorette ActiveStop is an advanced mobile and online behavioural support programme which has been devised by experts and is based on proven scientific principles, to help you give up smoking for good.
- ▶ It has been specially designed to be used alongside Nicorette and is on hand 24 hours a day through the internet and your mobile phone.
- ▶ Nicorette works with your body to help you deal with the physical craving for nicotine, whilst ActiveStop supports your mind to coach you all the way until you've stopped smoking. Call now on 0800 244 838.



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What will I get?

On your personalised ActiveStop web pages you'll have access to:

Diary
Through a series of daily tasks, we'll guide you through managing your thoughts, feelings and behaviour and how you can plan each day so that you are ready to face whatever arises.

Progress Monitor
The Progress Monitor brings together all of the headway you are making in one easy-to-view place. From how much money you're saving, to health facts and fitness levels, it will keep you motivated throughout the programme.

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Today's Articles

Daily articles cover a range of topics from the changes your body is undergoing to tips to cope with the inevitable cravings.

And the Craving Help-Line

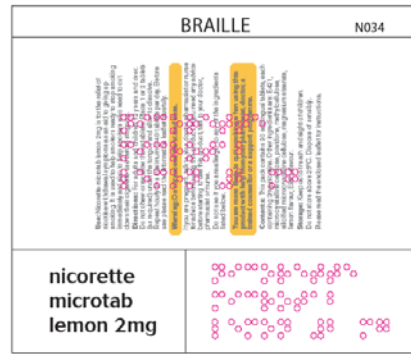
If ever you feel the urge to smoke you can call anytime day or night and by selecting the kind of problem you are experiencing, you'll be able to listen to relevant, on-the-spot advice.

Call now on 0800 244 838.



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COUNTRY: GB/England
 SIZE: 92 x 68 x 49 mm
 PMS COLORS: 2945, 2925, 143, 123, 348, black



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