

NICORETTE COMBI

UKPAR

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NICORETTE COMBI

LAY SUMMARY

On 7th May 2009, the MHRA granted Pharmacia Limited a Marketing Authorisation (licence) for the medicinal products Nicorette Combi (PL 00032/0504). This product is available on general sales licences (GSL). It is used to relieve withdrawal symptoms and reduce the cravings for nicotine that you get when you try to stop smoking.

Nicorette Combi consists of a patch and gum. When you apply a Nicorette Patch to the skin, nicotine is released and passes into your body through the skin. When you chew Nicorette Gum, nicotine is released and passes into your body through the lining of your mouth. The nicotine obtained from the combination of the patch and gum is sufficient to relieve the unpleasant withdrawal symptoms. It will also help to stop your craving to smoke, but will not give you the "buzz" you get from smoking a cigarette.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Nicorette Combi outweigh the risks, hence a Marketing Authorisation has been granted.

On 12th May 2009, a change of ownership was granted to change the marketing authorisation holder for this product from Pharmacia Limited to McNeil Products Limited (PL 15513/0356).

NICORETTE COMBI

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a Marketing Authorisation for the medicinal product Nicorette Combi to Pharmacia Limited (PL 00032/0504) on 7th May 2009. The product is available on general sales licences (GSL) for the relief of nicotine withdrawal symptoms as an aid to smoking cessation in adults and children over 12 years of age.

This is a line extension application submitted under Article 8.3, from Nicorette Mint 2mg Gum (PL 15513/0171) and Nicorette Patch 15mg (PL 15513/0177).

The product contains nicotine, as both a patch containing 15mg nicotine and a gum containing 2mg nicotine resinate. The product is indicated for the relief of nicotine withdrawal symptoms as an aid to smoking cessation in adults and children over 12 years of age, in smokers who have more than 10 cigarettes a day, experience acute or breakthrough cravings or fail with single treatment. The patch provides background nicotine levels while the gum is used for immediate relief of cravings. If possible, Nicorette Combi should be used in conjunction with a behavioural support programme.

On 12th May 2009, a change of ownership was granted to change the marketing authorisation holder for this product from Pharmacia Limited to McNeil Products Limited (PL 15513/0356).

PHARMACEUTICAL ASSESSMENT

As the gum and the patch are identical to Nicorette Mint 2mg Gum (PL 15513/0171) and Nicorette Patch 15mg (PL 15513/0177), which have already been granted licences by the MHRA, no new pharmaceutical data have been submitted for this application and none are required.

PRECLINICAL ASSESSMENT

As the gum and the patch are identical to Nicorette Mint 2mg Gum (PL 15513/0171) and Nicorette Patch 15mg (PL 15513/0177), which have already been granted licences by the MHRA, no new preclinical data have been submitted for this application and none are required.

CLINICAL ASSESSMENT

1. CLINICAL PHARMACOLOGY

The pharmacodynamics and pharmacokinetics of nicotine are covered in the original applications for the gum and patch. The pharmacokinetics of the combination are discussed in the clinical expert report for this product.

Nicotine gum 2mg, taken as required, is said to result in nicotine levels that are approximately one-third of those achieved during cigarette smoking. The nicotine patch generally results in nicotine substitution of some 50-60%.

The combination provides a passive delivery system (patch) which results in a gradual rise in nicotine levels over some 6-10 hours, and the additional more rapid absorption from the 'self-administered' gum which has an effect within 5-7 minutes of starting to chew.

2. EFFICACY

The clinical program consisted of one exploratory Phase II study, two pivotal Phase III studies and eight supportive Phase III studies. These were conducted from 1991-1999 and included data from nearly 4000 patients.

Exploratory study T91NT09: This was a Phase II double-blind, placebo-controlled crossover study in 28 volunteer smokers. Subjects abstained from smoking during 4 x 3-day treatment periods (double active gum + patch, active patch + placebo gum, active gum + placebo patch and double placebo), and smoked for 4 days between treatments.

Analysis of withdrawal symptoms, rated on a VAS, showed the double active to be significantly superior ($p < 0.001$) to the patch or gum individually, whilst each individual treatment was superior to the double placebo ($p < 0.001$). The baseline score when smoking was 101.1, but 187 during abstinence (double placebo). In the active gum period this was 142.0, active patch was 128.3 and using both actives was 99.2; comparable, therefore, to smoking as regards the relief of withdrawal symptoms.

Cotinine levels were taken as an indicator of nicotine intake: nicotine substitution was estimated at 79% for the double active, 49% for the patch alone and 45% for the gum alone. An average of 5-6 pieces of gum were chewed daily, higher than that shown in the pivotal studies, but this was thought to have been due to the much shorter treatment period.

Pivotal studies: Both pivotal studies were double-blind, placebo-controlled and involved male and female subjects who had smoked for longer than 3 years and who wished to stop smoking. During the first 12 weeks, the subjects used one patch a day and were instructed to chew 4 pieces of gum ad lib. Patch use was then tapered using the lower dose (or matched placebo) patch over a period of 12 weeks in T91NT08 and 6 weeks in T91NT12. Gum use was allowed for up to 12 months. Subjects still using gum after 6 months were encouraged to stop or to reduce the dose.

The primary efficacy parameter was sustained abstinence from smoking, strictly defined as complete self-reported abstinence after the first week, verified by expired

CO levels <10parts per million (ppm). Salivary cotinine was measured as an indicator of nicotine uptake. Analyses were performed on an intent-to-treat basis and the studies were powered to detect significant differences between treatment groups for up to 3 months.

T91NT08: This study enrolled 374 adult smokers, randomised to receive either nicotine patch 15mg/16 hours + nicotine gum 2mg or nicotine patch + placebo gum or double placebo.

Abstinence rates with the combination were significantly superior ($p < 0.05$) to both nicotine patch + placebo and double placebo for up to 6 months. After 1 week, nicotine substitution was estimated to be 62% for the active combination and 40% for the patch alone.

T91NT12: This study enrolled 300 adult smokers, randomised to receive either nicotine patch 15mg/16hr + nicotine gum 2mg or placebo patch + nicotine gum.

Abstinence rates with the combination were significantly superior ($p = 0.038$) to placebo patch + nicotine gum for 12 weeks. After 1 week, nicotine substitution was estimated to be 59% for the active combination and 28% for the gum alone.

Other supportive studies are fully reported in the clinical expert report and accompanying dossier. These included various combinations of fixed-dose and flexible nicotine replacement therapy (NRT), utilising nicotine nasal sprays, patches, inhalers and gum (4mg).

3. SAFETY

No new safety issues have been raised by the studies performed in support of this application.

4. EXPERT REPORT

The clinical expert report has been written by a suitably qualified physician and is a satisfactory summary of the clinical aspects of the dossier.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The summary of product characteristics is consistent with those for the reference products and is satisfactory.

6. PATIENT INFORMATION LEAFLET (PIL)

The patient information leaflet is consistent with those for the reference products and is consistent with the details of the summary of product characteristics.

7. LABELLING

The labelling is medically satisfactory.

8. BENEFIT-RISK ASSESSMENT

The benefit–risk assessment for this product is considered to be positive.

9. CONCLUSIONS

The grant of a licence for this product is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY

The important quality characteristics of Nicorette Combi 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.

PRECLINICAL

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

EFFICACY

Clinical studies have been submitted, showing superiority of the Nicorette Combi over nicotine patches or nicotine gum alone (or placebo) in maintaining abstinence rates from smoking.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference products, Nicorette Mint 2mg Gum (PL 15513/0171) and Nicorette Patch 15mg (PL 15513/0177).

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with nicotine is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

NICORETTE COMBI**STEPS TAKEN FOR ASSESSMENT**

1	The MHRA received the Marketing Authorisation applications on 1 st July 2003
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 12 th February 2009
3	A request for further information was made concerning the pharmaceutical data on 2 nd March 2009
4	A response to the request for further information was received on 18 th March 2009
5	The applications were determined on 7 th May 2009

NICORETTE COMBI**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

Date submitted	Application type	Scope	Outcome

1 NAME OF THE MEDICINAL PRODUCT

Nicorette Combi

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Patch: Nicotine, 15mg released over 16 hours use. Each patch is 30 sq.cm, containing nicotine 0.83mg/sq.cm.

Gum: Contains 2mg nicotine, as nicotine resinate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal Patch

An opaque, beige, square patch.

Medicated Chewing Gum

A square, beige piece of gum

4 CLINICAL PARTICULARS**4.1 Therapeutic indications**

Nicorette Combi 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 used for smokers who smoke more than 10 cigarettes per day, individuals who experience acute or breakthrough cravings, or those who have failed with single treatment. The patch provides background nicotine levels while the gum is used for immediate relief of cravings. Combination treatment has been shown to have greater success rates than either patch or gum alone.

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

4.2 Posology and method of administration

Nicorette Combi is a smoking cessation preparation consisting of a 15mg/16 hour patch and a 2mg chewing gum. The patient should initially use the patch and gum together to control cravings. After 12 weeks of treatment, the patch should be discontinued and the patient should be weaned off nicotine using the gum only – see table below.

The patient should make every effort to stop smoking completely during treatment with this product.

Adults (over 18 years of age)**Patch**

The patch should be applied to clean dry intact areas of hairless skin, for example on the hip, upper arm, or chest. These areas should be varied each day and the same site should not be used on consecutive days. There is no clinically significant difference in bioavailability of nicotine when the patch is applied to either the hip, upper arm or chest.

Cut open the pouch with scissors along the line, as indicated. The transparent plastic backing is peeled away and the patch pressed carefully onto the skin. The fingers should be rubbed firmly around the edge to ensure that the patch sticks properly. The patch will normally resist bathing, showering, or swimming, but if it does come off it should be replaced with a new one. Use of skin oils or talc can prevent proper adhesion of the patch.

It is intended that the patch be worn through the waking hours (approximately 16 hours) being applied on waking and removed at bedtime. After 12 weeks the patch should be discontinued. See the following table for more detail.

Gum

The gum should be used whenever there is an urge to smoke according to the ‘chew and rest’ technique described on the pack. After about 30 minutes of such use, the gum will be exhausted. Use a minimum of four 2mg gums per day; usually 5 – 6 gums will be adequate for effect. Not more than 15 pieces of the chewing gum may be used each day. Absorption of nicotine is through the buccal mucosa, any nicotine that is swallowed being destroyed by the liver.

Weaning

For patients who have successfully abstained from smoking for 12 weeks using Nicorette Combi, the patches should be discontinued and the patient should be supported through a further 6-12 week weaning period using the same dosage of gum as in the initial treatment phase. The amount of gum used is then gradually reduced up to 9 months from the start of treatment. When daily use is 1-2 gums, use should be stopped.

Any spare gum should be retained as a craving may suddenly return.

Adults who use NRT beyond 9 months for smoking cessation are recommended to seek additional help and advice from a healthcare professional.

Initial treatment		
Initial treatment period	Patch	Mint 2mg Gum
First 12 weeks	1 patch 15mg/16 hours per day	Ad libitum. Recommended 5 – 6 gums per day. Maximum 15 gums per day.
Weaning period		
Next 6-12 weeks	Patch not applied	Ad libitum. Recommended 5 – 6 gums per day. Maximum 15 gums per day.
Up to 9 months from the start of treatment	Patch not applied	Gradually wean from gum use

Adolescents (12 to 18 years)

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

The dose and method of use are as for adults. However, 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.

The 12 week period should be made up as follows. For the first eight weeks, both the patch and gum should be used. The use of patch should be discontinued after this period. For the remaining 4 weeks, only the gum should be used and the amount should be gradually reduced until daily use is only 1-2 gums. At this point, gum use should be discontinued completely.

4.3 Contraindications

Hypersensitivity to nicotine or any other component of the patch or gum.

4.4 Special warnings and precautions for use

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

Underlying cardiovascular disease: In stable cardiovascular disease Nicorette Combi 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 Combi 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 or hepatic impairment: Nicorette Combi 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. After removal, the patch should be folded in half, adhesive side innermost, and placed inside the opened sachet, or in a piece of aluminium foil. The used patch should then be disposed of carefully, away from the reach of children or animals. The gum should also be disposed of with care.

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

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

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

Patch only

Generalised dermatological disorders: Patients with chronic generalised dermatological disorders such as psoriasis, chronic dermatitis or urticaria should not use the patch.

Erythema may occur. If it is severe or persistent, treatment should be discontinued.

Gum only

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.

Denture warning: Smokers who wear dentures may experience difficulty in chewing the gum. The chewing gum may stick to, and may in rare cases damage dentures.

Excipients: The gum also contains butylated hydroxytoluene (E321); this may cause irritation to the mucous membranes.

Special warnings and precautions for the combination of nicotine gum with nicotine patch are the same as those for each treatment alone.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

Pregnancy

Nicorette Combi should not be used in pregnancy or lactation. However, NRT monotherapy may be recommended dependent on a risk benefit assessment.

4.7 Effects on ability to drive and use machines

Not applicable.

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 Combi 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 Combi has not been found to cause any serious adverse effects. Most of the undesirable effects reported by patients occur during the first few weeks after start of treatment. About 20% of patch users experience mild local skin reactions during the first few weeks of treatment.

Excessive use of Nicorette Combi by those who have not been in the habit of inhaling tobacco smoke could possibly lead to nausea, faintness or headaches.

Nicotine from the gum may sometimes cause a slight irritation of the throat at the start of treatment and may also cause increased salivation. Excessive swallowing of dissolved nicotine may, at first, cause hiccupping.

The chewing gum may stick to, and may in rare cases damage dentures.

Reported adverse events associated with 5mg, 10mg and 15mg patch include:

<u>Body System</u>	<u>Incidence*</u>	<u>Reported adverse event</u>
Nervous system disorders:	Common:	Dizziness, headache
Cardiac disorders:	Uncommon:	Palpitations
	Very rare:	Reversible atrial fibrillation
Gastrointestinal disorders:	Common:	Gastrointestinal discomfort, nausea, vomiting
Skin and subcutaneous tissue disorders:	Uncommon:	Urticaria
General disorders and administration site disorders:	Very common:	Itching
	Common:	Erythema

Reported adverse events associated with 2mg and 4mg gum include:

<u>Body System</u>	<u>Incidence*</u>	<u>Reported adverse event</u>
Nervous system disorders:	Very common:	Headache
	Common:	Dizziness
Cardiac disorders:	Uncommon:	Palpitations
	Very rare:	Reversible atrial fibrillation
Gastrointestinal disorders:	Very common:	Gastrointestinal discomfort, hiccups, nausea,
	Common:	Vomiting
Skin and subcutaneous tissue disorders:	Uncommon:	Erythema, urticaria
General disorders and administration site disorders:	Very common:	Sore mouth or throat, jaw-muscle ache
	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.

Adverse reactions that may occur when using the combination treatment (patch and gum) only differ from each treatment alone in terms of local adverse events associated with the formulations. The frequencies of these adverse events are comparable to those reported in the SPCs for the respective Nicorette products.

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

The pharmacological effects of nicotine are well documented. Owing to its many actions, the overall effects of nicotine are complex. The response at any one time represents a summation of stimulant and depressant actions from direct, reflex and chemical mediator influences on several organs. The main 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. Nicotine acts on specific binding sites or receptors throughout the nervous system.

5.2 Pharmacokinetic properties

Pharmacokinetic properties of Nicorette Patch

Taking into account the residual concentration of nicotine in the transdermal system, the nicotine released from the system is efficiently absorbed: a bioavailability of between 80-100% has been reported. There is no clinically significant difference in bioavailability of nicotine when the patch is applied to either the hip, upper arm or chest.

Steady state concentrations of plasma nicotine in volunteers were examined during a study period of six days. Although nicotine was detectable 24 hours after the first dose, the data did not indicate any accumulation.

T_{max} of nicotine after application of a 30cm² nicotine transdermal system has been shown to vary between 6 ± 2 and 9 ± 3 hours: C_{max} has been shown to vary between 13 ± 3 and 16 ± 5ng/ml. No differences in these pharmacokinetic parameters have been observed between males and females.

All Nicorette Patches are labelled by the average amount of nicotine absorbed by the patient over 16 hours.

Pharmacokinetic properties of Nicorette chewing gum.

Nicotine administered in chewing gums is readily absorbed from the buccal mucous membranes. Demonstrable blood levels are obtained within 5 – 7 minutes and reach a maximum about 30 minutes after the start of chewing. Blood levels are roughly proportional to the amount of nicotine chewed and have been shown never to exceed those obtained from smoking cigarettes.

Pharmacokinetic properties of the Combination of Nicorette patch and Nicorette chewing gum.

The plasma levels of nicotine when combining one 15mg patch and 2mg chewing gums will depend on the number of chewed gums and the dosing interval.

The combination of the 15mg/16 hour patch and twenty four 2mg gums, i.e. 1 patch + 24 gums per 16 hours resulted in maximum plasma levels of about 39 ng/mL.

A simulation of plasma concentrations shows that if one 15mg/16 hour patch is applied in the morning and five to six 2mg chewing gums are evenly distributed over the awake hours according to the recommended dosage, a maximum plasma level of about 19 - 20ng/mL will be reached. The simulation is based on nicotine pharmacokinetics upon separate use of the 15mg patch and 2mg gums, respectively.

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

Patch:

Adhesives

Medium molecular weight polyisobutylene

Low molecular weight polyisobutylene

Polybutylene

Non-woven contact laminate

Polyester

Release liner

Siliconised polyester

Backing film

Polyester

Gum:

Chewing gum base, containing butylated hydroxytoluene (E321)

Xylitol

Sodium carbonate, anhydrous

Sodium hydrogen carbonate

Peppermint oil

Levomenthol

Magnesium oxide, light

Talcum

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 months

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Patches: Heat sealed multilaminate pouch containing one patch. Gums: PVC/PVDC/Al blister packed strips each containing 15 pieces of gum.

Each Nicorette Combi pack contains 14 patches and 90 gums.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

Patches:

Nicotine residues in the used patches may present a hazard to children and pets, thus used patches should be folded, sticky sides together, put back in an empty pouch and placed in household rubbish.

Gum:

Dispose of the gum sensibly.

See section 4.4.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

PL 15513/0356

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**10 DATE OF REVISION OF THE TEXT**

January 2009

(Nicorette Logo)**ActiveStop**

Supporting you, body and mind

Personalised Support programme

Enrol on the internet or call now on 0800 244 838.

Nicorette Combi

nicotine

transdermal patch & medicated chewing gum

A guide for users

What should you know about Nicorette Combi

Nicorette

15mg Patch

(15mg nicotine transdermal patch)

Nicorette

Mint 2mg Gum

(2mg nicotine medicated chewing gum)

Low strength

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
- 2** Before using this medicine
 - Do not use Nicorette Combi
 - Talk to your doctor, nurse or pharmacist
 - If you are pregnant or breast-feeding
 - Some of the ingredients can cause problems
- 3** How and when to use this medicine
 - How to use Nicorette Combi
 - When to use Nicorette Combi
 - How to stop smoking
 - o Stopping immediately
 - o Adults aged 18 years and over
 - o Children aged 12 years and over
 - If you have used too much Nicorette Combi
 - If a child has used or swallowed Nicorette Patch or Gum
- 4** Possible side-effects
- 5** Storing and disposal
- 6** Further information
- 7** Helpful tips on giving up
- 8** Nicorette ActiveStop

1 What this medicine is for

Nicorette Combi 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.

To help 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.

Nicorette® 15mg Patch: Each patch releases 15 milligrams of nicotine, the active ingredient, over 16 hours.

Nicorette® Mint 2mg Gum: Each gum releases 2 milligrams of nicotine, the active ingredient.

What does Nicorette Combi 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 apply a Nicorette Patch to the skin, nicotine is released and passes into your body through the skin. When you chew Nicorette Gum, nicotine is released and passes into your body through the lining of your mouth. The nicotine obtained from the combination of the patch and gum is sufficient to relieve the unpleasant withdrawal symptoms. It will also help to stop your craving to smoke, but will not give you the "buzz" you get from smoking a cigarette.

For the best effect, ensure that you apply the Nicorette Patch correctly and chew the gum according to the Nicorette Chewing Technique – see *"How to Use Nicorette Combi."*

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

[X] Do not use Nicorette Combi:

- if you have an allergy to nicotine or any of the other ingredients.
- if you are pregnant or breast-feeding – see page X

[!] 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 X 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 a stomach ulcer, duodenal ulcer, inflammation of the stomach or inflammation of the oesophagus (passage between the mouth and stomach).
- if you have liver or kidney disease.
- if you have an overactive thyroid gland or have a *phaeochromocytoma* (a tumour of the adrenal gland that can affect blood pressure) – your doctor will have told you this.
- if you have diabetes – monitor your blood sugar levels more often when starting to use Nicorette Combi as you may find your insulin or medication requirements alter.
- if you have a skin disorder such as psoriasis, eczema or hives (urticaria) covering a large area of your skin.
- if you are taking any other medicines such as theophylline, clozapine or ropinirole. Stopping smoking may require the dose of these medicines to be adjusted.

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

[!] If you are pregnant or breast-feeding

If you are pregnant or breast-feeding: you should not use Nicorette Combi. Although ideally you should try to give up smoking without NRT, some NRT products may be suitable. You should talk to your doctor, nurse or pharmacist for advice.

[!] Some of the ingredients can cause problems

The chewing gum base contains butylated hydroxytoluene (E321), an antioxidant. This may cause local skin reactions (e.g. contact dermatitis) or irritation to the eyes and mucous membranes.

3 How and when to use this medicine

[i] How to use Nicorette Combi

Follow the instructions below.

Nicorette Patch

Choosing where to apply the patch

- 1** Before applying your Nicorette Patch, choose a completely clean, dry area of hairless skin on the front or side of the chest, upper arm or hip.
- 2** Avoid placing the patch onto any area of skin that is red, cut or irritated.
- 3** Do not apply oil or talcum powder to the skin before putting on the patch as this may prevent it from sticking properly.

- 4** It is important that you do not use the same area on two consecutive days to help avoid irritating that site.

How to apply the patch

- 1** Each patch comes in a child resistant sachet, which can be opened by cutting along the edge with a pair of scissors.
- 2** Remove the patch from its sachet and then remove the clear plastic backing.
- 3** Apply the patch firmly by pressing the sticky side of the patch to the chosen area of skin. Run your finger around the edge of the patch to ensure it sticks properly.

[i] Removing and disposing of the patch

- 1** The patch should be removed before you go to bed as Nicorette Patch is not designed to be worn when you go to sleep at night or for more than 16 hours each day.
- 2** After removal, the patch should be folded in half, sticky side inwards and placed inside the opened sachet or a piece of aluminium foil.
- 3** The patch should then be disposed of carefully in the household rubbish, out of reach of children and animals.

Nicorette Gum

[i] How to chew Nicorette Gum - The Nicorette Chewing Technique

The method of chewing Nicorette Gum is not the same as for ordinary chewing gum. Nicorette Gum is chewed to release nicotine then rested so that nicotine can be taken in through the lining of the mouth. If Nicorette Gum is chewed continuously, the nicotine is released too quickly and is swallowed. This may irritate your throat, upset your stomach or give you hiccups.

If you have false teeth you may have difficulty chewing the gum as Nicorette Gum could stick to them and on rare occasions, damage dentures. If you experience a problem, other types of nicotine replacement therapy such as a skin patch, inhalator or microtab may be more suitable for you.

[i] The Nicorette Chewing Technique

1 Chew slowly until taste becomes strong.

2 Rest between gum and cheek.

3 Chew again when the taste has faded.

Keep chewing like this for about half an hour. After this time the gum will have lost its strength and you should dispose of it carefully.

When to use Nicorette Combi

Nicotine replacement therapy often provides sufficient nicotine when used as single therapy. Smokers who smoke more than 10 cigarettes per day, people who experience breakthrough cravings, or those who have failed to stop smoking using single NRT may benefit from using Nicorette Combi.

Below is the dosage information for Nicorette Combi. This shows the number of patches and gums you should be using, when you should use them and the maximum amount of time you should be using nicotine replacement therapy for.

- You must stop smoking completely before using Nicorette Combi.
- You should use the gum and patch at the same time.

[i] Children under 12 years

Do not give this product to children under 12 years.

[i] Adults and children aged 12 years and over

Age	Dosage of Patch	Dosage of Gum
Adults and children aged 12 years and over	Apply one new patch to the skin when you wake (usually in the morning). Remove 16 hours later which is usually at bedtime.	One as required to relieve cravings.
<ul style="list-style-type: none"> - Use only one patch and one piece of gum at a time. - If you lose a patch whilst swimming, bathing or showering, you can replace it with another patch. - Dispose of patches carefully after you have removed them, ensuring they are out of the reach of children and pets - You should use at least 4 pieces of gum per day. Most people use between 5 and 6 gums per day. - Do not use more than 15 gums per day. - Children aged 12 up to 18 years should not use for longer than 12 weeks without asking for help and advice from a doctor, nurse or pharmacist. - Adults aged 18 years and over should not use for longer than 9 months without asking for help and advice from a doctor, nurse or pharmacist. 		

[i] How to stop smoking

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.

If you find it hard to stop smoking using Nicorette Combi, you are worried that you will start smoking again without it, or you find it difficult to reduce the amount of Nicorette Combi you are using, talk to your **doctor, nurse or pharmacist**. Remember Nicorette Combi is not intended as a substitute for smoking, it is to be used as an aid to giving up.

[i] Stopping Immediately

The idea is to stop smoking immediately and use Nicorette Patch and Gum together to relieve cravings to smoke. After 12 weeks of using both the Nicorette Patch and Nicorette Gum, the patch is discontinued. Only the Nicorette Gum is used for the remainder of the treatment period. The dosage is gradually reduced until you can stop using the gum altogether.

[i] Adults aged 18 years and over

See the following diagram which shows the basic step by step process. Make sure that you read the instructions for each step in the information which follows.

Preparation	12 weeks (3 months)	6-12 weeks	Up to 9 months from the start of treatment
Step 1	Step 2	Step 3	Step 4

Step 1: Set a date to quit and stop smoking cigarettes.

Step 2: Use the patch and gum together for 12 weeks (3 months). The gum should be used to relieve your cravings to smoke. See the dosing table in "When to use Nicorette Combi" on page X to see how often you can use the patch and gum.

Step 3: If you have remained free of cigarettes at week 12, stop using the patch. You should continue to use as many gums as you were using during Step 2.

Step 4: Start to reduce the number of gums you use. You should try to use fewer pieces each day. When you are using only one or two pieces of gum per day, you should completely stop.

- **If you need to use the product for longer than 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 Nicorette Combi. Remember you can use nicotine replacement therapy again if this should happen.**

[i] Children 12 years and over

See the following diagram which shows the basic step by step process. The times given below are the longest amount of time they should take and you should try to achieve your move to the next step in the shortest time possible.

Make sure that you read the instructions for each step in the information which follows.

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

Step 1: Set a date to quit and stop smoking cigarettes.

Step 2: Use the patch and gum together for 8 weeks (2 months). The gum should be used to relieve your cravings to smoke. See the dosing table in "When to use Nicorette Combi" on page X to see how often you can use the patch and gum.

Step 3: Stop using the patch and start to reduce the number of gums you use over a period of four weeks. You should try and use fewer pieces of gum each day. When you are using only one or two pieces of gum per day, you should stop completely.

Do not use for longer than 12 weeks in total without asking for help and advice from your doctor, nurse or pharmacist.

[i] If you have used too much Nicorette Combi?

If you have used more than the recommended amount of Nicorette Patch or Nicorette Gum, left the patch on for too long, or have smoked whilst using Nicorette Combi, you may experience nausea (feeling sick), salivation, pain in your abdomen, diarrhoea, sweating, headache, dizziness, hearing disturbance or weakness.

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

[i] If a child has used or swallowed a Nicorette Patch or Gum

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

Nicotine ingestion by a child may result in severe poisoning.

4 Possible side-effects

Like all medicines, Nicorette Combi can have side-effects. As many of the effects are due to nicotine, they can also occur when nicotine is obtained by smoking.

Effects related to stopping smoking (nicotine withdrawal)

You may experience unwanted effects because by stopping smoking you have reduced the amount of nicotine you are taking. You may also experience these effects if you under use Nicorette Combi 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.

These effects include:

- feeling faint
- feeling sick (*nausea*)
- headache

Side-effects of Nicorette Gum

Nicorette Gum can sometimes cause a slight irritation of the throat at the start of the treatment. It may also cause increased salivation. The gum may occasionally stick to dentures and in rare cases damage them. Excessive swallowing of the nicotine released from the gum may result in hiccupping.

Side-effects of Nicorette Patch

When you use the Nicorette Patch for the first time it may cause a mild skin reaction. This is usually redness or itching of the skin where the patch has been. This will usually disappear after a few days. Rarely the reaction may persist or if there is a more severe skin reaction, you should stop using the patches and consult a doctor, nurse or pharmacist.

Overall side-effects for Nicorette Combi**Very common side-effects**

(more than 1 in every 10 people are affected)

- itching – this usually disappears within a few days
- headache
- sore mouth or throat
- jaw-muscle ache
- stomach discomfort
- feeling sick (nausea)
- hiccups

Common side-effects:

(less than 1 in every 10 people are affected)

- dizziness
- sickness (vomiting)
- redness of the skin – this usually disappears within a few days

Uncommon side-effects:

(less than 1 in every 100 people are affected)

- hives (urticaria)
- chest palpitations

Rare side-effects:

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

- allergic reactions (swelling of the mouth, lips, throat and tongue, itching of the skin, swelling of skin, ulceration and inflammation of the lining of the mouth).

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.

5 Storing and disposal

- **Keep Nicorette Combi out of the reach and sight of children and animals.**

Nicotine in high doses can be very dangerous and sometimes fatal if taken by small children.

- Do not store Nicorette Combi above 25°C.
- Do not use the gum or the patch after the 'Use before' date on the box, blister strip or sachet.
- Dispose of Nicorette Patches and Gum sensibly away from children and animals. Dispose of Nicorette Patch as directed by folding it in half and placing inside the empty sachet (or wrapping in a piece of aluminium foil) before throwing away. Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 Further information

What's in this medicine?

The active ingredient is nicotine. Each patch releases 15 milligrams of nicotine, over 16 hours. Each gum contains 2 milligrams of nicotine (as nicotine resin).

Other ingredients of the patch are:

Medium molecular weight polyisobutylene, low molecular weight polyisobutylene, polybutylene, siliconised polyester release liner, polyester non-woven contact laminate, polyester backing film.

Other ingredients of the gum are:

Chewing gum base, xylitol, sodium carbonate, sodium hydrogen carbonate, peppermint oil, levomenthol, magnesium oxide and talc. The chewing gum base contains butylated hydroxytoluene (E321), an anti-oxidant.

What the medicine looks like

Nicorette patch is packed into individual sachets. The gums are blister packed in strips of 15 gums.

Each Nicorette Combi pack contains 14 patches and 90 gums.

Who makes Nicorette Combi?

The Product Licence holder is Pharmacia Limited, Sandwich, Kent, CT13 9NJ, UK.

The manufacturer is McNeil AB, Helsingborg, Sweden.

This leaflet was revised in March 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.

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.

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.

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 close 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 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 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 emphasise 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.

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 or in the pub – 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 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 few pages. This is a personalised support programme which works with Nicorette to support you, with the aim of helping you give up smoking. All you need is internet access and a mobile telephone.

8 Nicorette ActiveStop [ActiveStop Logo]

Personalised support programme
Enrol on the internet or call now on 0800 244 838.

How can ActiveStop help me?

- Nicorette ActiveStop is an advanced, interactive online programme with mobile phone support. It 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 gives you practical daily support coaching you all the way until you've stopped smoking.

Call now on 0800 244 838.
[ActiveStop]

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.

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.

Nicorette Combi CartonFront panel

Nicorette Combi
nicotine

15mg patch
mint 2mg gum

14 patches
Mint flavour sugar-free gum 90 pieces

Helps overcome your urge to smoke

Side panel 1

Nicorette Combi
nicotine

15mg patch
Mint 2mg gum

15mg patch 14 patches
Mint 2mg gum 90 pieces sugar-free

Side panel 2

Nicorette Combi
nicotine

15mg patch
Mint 2mg gum

15mg patch 14 patches
Mint 2mg gum 90 pieces sugar-free

Top panel

Nicorette Combi
nicotine

15mg patch
Mint 2mg gum

15mg patch 14 patches
Mint 2mg gum 90 pieces sugar-free

Bottom panel

Batch No:

Use before:

Barcode

Back panel

Use: Nicorette Combi (15mg patch and mint 2mg gum) is for the relief of nicotine withdrawal symptoms as an aid to giving up smoking. The patch is used to administer a background nicotine level which provides continuous craving relief. The gum is used to control breakthrough cravings.

Directions: For adults and children 12 years and over. Stop smoking completely before using Nicorette Combi. Please read the enclosed leaflet carefully before starting to use the product. Apply the patch to a clean, dry area of skin in the morning and remove the patch 16 hours later. Chew one piece of gum when you feel the urge to smoke – most people use about 5-6 pieces a day. Do not use more than 15 pieces a day. Please note the chewing technique below.

Warning: Do not exceed the stated dose.

Nicorette Chewing Technique:

1. Chew slowly until taste becomes strong.
2. Rest between gum and cheek.
3. Chew again when taste has faded.

Do not use this product if you are pregnant or breast-feeding.

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

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

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

Contents: This pack contains fourteen 30 cm² transdermal patches, each containing nicotine 0.83 mg/cm² (once-daily patch for application to the skin, releasing 15 mg over 16 hours). Other ingredients are: Medium molecular weight polyisobutylene, low molecular weight polyisobutylene, polybutylene, siliconised polyester release liner, polyester non-woven contact laminate, polyester backing film.

This pack also contains 90 pieces of mint flavour chewing gum, each containing 2 mg nicotine (as nicotine resinate). Also includes: chewing gum base, xylitol, sodium carbonate, sodium bicarbonate, peppermint oil, levomenthol, magnesium oxide, talc and E321.

Storage: Keep out of the reach and sight of children. Do not store above 25°C.

Dispose of sensibly.

PL 00032/0504

PL Holder: Pharmacia Limited, Sandwich, Kent, CT13 9NJ, UK

Foil for Gum

Nicorette Combi
mint 2mg gum
nicotine

Pharmacia

Batch Number:
Use before: MM/YYYY

Laminate for Patch

Front
Nicorette Combi
Nicotine

16 hours

Transdermal patch

Pharmacia

Back
Batch:
Use Before:

Each patch contains nicotine 24.9 mg releasing 15 mg nicotine over 16 hours.

$30 \text{ cm}^2 = 24.9 \text{ mg}$

Keep out of the reach and sight of children.