COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Etos Nicotine mint 2 mg and 4 mg lozenges (nicotine)

NL/H/4748/001-002/DC

Date: 6 March 2023

This module reflects the scientific discussion for the approval of Etos Nicotine mint 2 mg and 4 mg lozenges. The procedure was finalised in the United Kingdom (UK/H/4556/001-002/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

ASDA / NICAID / MORRISON'S / SUPERDRUG / SAINSBURY'S / WILKO / PARAMED NICOTINE 2MG AND 4MG LOZENGES
PL 12063/0068-69

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LAY SUMMARY

The MHRA granted Wrafton Laboratories Ltd a Marketing Authorisation (licence) for the medicinal products Asda / NicAid / Morrison's / Superdrug / Sainsbury's / Wilko / Paramed Nicotine 2mg and 4mg Lozenges (PL 12063/0068-9) on the 26th February 2007. This general sales list (GSL) medicine is indicated for the relief of nicotine withdrawal symptoms including cravings associated with smoking cessation. Nicotine 2 mg and 4mg Lozenges should preferably be used in conjunction with a behavioural support programme.

Asda / NicAid / Morrison's / Superdrug / Sainsbury's / Wilko / Paramed Nicotine 2mg and 4mg Lozenges contains the active ingredient nicotine resinate as either a 2mg lozenge or a 4mg lozenge.

The data presented to the MHRA, pre-licensing, demonstrated that Asda / NicAid / Morrison's / Superdrug / Sainsbury's / Wilko & Paramed 2mg and 4mg Lozenges is essentially similar or equivalent to the approved product Niquitin CQ 2mg/4mg lozenges (PL 00079/0369 and 0370 respectively) licensed 24/09/01, which is part of the same global marketing authorisation as Niquitin CQ Patch 14 mg (PL 00079/0346).

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of Asda / NicAid / Morrison's / Superdrug / Sainsbury's / Wilko / Paramed Nicotine 2mg and 4mg Lozenges outweighs the risks, hence a Marketing Authorisation has been granted.

ASDA / NICAID / MORRISON'S / SUPERDRUG / SAINSBURY'S / WILKO / PARAMED NICOTINE 2MG AND 4MG LOZENGES PL 12063/0068-69

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 to Wrafton Laboratories Ltd Marketing Authorisations (licenses) for the medicinal product Asda / NicAid / Morrison's / Superdrug / Sainsbury's / Wilko / Paramed 2mg and 4mg Nicotine Lozenges on the 26th February 2007. This product is a general sales list medicine (GSL).

This application was submitted as a standard and a complex national abridged Marketing Authorisation Application according to Directive 2001/83/EC, claiming essential similarity to the approved product Niquitin CQ 2mg/4mg lozenges (PL 00079/0369 and 0370 respectively), licensed 24/09/01, which is part of the same global marketing authorisation as Niquitin CQ Patch 14 mg (PL 00079/0346).

This product contains the active ingredient nicotine and is indicated for the relief of nicotine withdrawal symptoms including cravings associated with smoking cessation. Nicotine 4 mg Lozenges should preferably be used in conjunction with a behavioural support programme.

PHARMACEUTICAL ASSESSMENT

3.2.S. DRUG SUBSTANCE

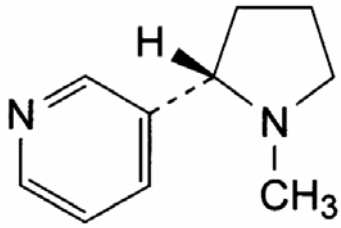
GENERAL INFORMATION

Nicotine Resinate is the subject of a Drug Master File.

BAN/INN: Nicotine Resinate

Definition: Nicotine (3-[(2S)-1-methylpyrrolidin-2-yl] pyridine) with a weak cationic exchange resin (Polacrilex, a cross linked co-polymer of divinylbenzene and methacrylic acid).

Nicotine (15% w/w of nicotine resinate)



$C_{10}H_{14}N_2$ 162.2g/mol

There is no strict molecular formula for Nicotine Resinate. In this instance, Nicotine Resinate (also known as Polacrilex) contains 15% nicotine, 24% glycerol (glycerine/glycerolum $C_3H_8O_3$) with the rest being the polacrilex polymer.

Nicotine resinate is a white or slightly yellowish powder that is practically insoluble in water.

MANUFACTURE

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

CHARACTERISATION

Elucidation of the structure of the drug substance has been carried out in accordance with the USP method. The Finished Product Manufacturer also states that analysis for section 3.2.S.4 (controls of drug substance) confirms structure. Under 3.2.S.4 the substance is identified using Ph Eur identification tests therefore given the nature of the active and its manufacture, acceptable proof of structure is provided.

Potential isomerisation of the nicotine is addressed.

The typical impurity profile for Nicotine Polacrilex is presented. Structures are provided for all the impurities. Reference standards are provided.

CONTROL OF DRUG SUBSTANCE

The drug substance specification is in line with relevant guidance and pharmacopoeial requirements.

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

The reference standards used were provided. Whilst the reference standards for the impurities were not especially pure, they were only used to confirm specificity of a method which is acceptable.

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

Satisfactory packaging details have been provided for the container-closure system.

Appropriate stability data have been generated supporting a retest period of 2 years. .

3.2.P. DRUG PRODUCT

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Other ingredients consist of pharmaceutical excipients, namely mannitol, magnesium stearate, sodium alginate, xanthan gum, potassium bicarbonate, sodium carbonate anhydrous, aspartame and peppermint flavour. No overages are included.

All excipients used comply with their respective Ph Eur monograph, with the exception of the peppermint flavour (which complies with an in-house specification).

No preservatives are included in the product and the applicant states that microbial qualities are assessed during formal stability studies. This is acceptable.

Satisfactory certificates of analysis have been provided for all excipients. None of the excipients used contain material of animal or human origin.

Details of the development batches have been provided and of the batch used for the bioequivalence study.

PHARMACEUTICAL DEVELOPMENT

Satisfactory pharmaceutical development details have been provided.

MANUFACTURE

A valid manufacturing authorisation for the finished product manufacturer has been supplied. A description and flow-chart of the manufacturing method has been provided. The maximum batch size is stated. The applicant has provided an acceptable batch formula.

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

CONTROL OF DRUG PRODUCT

There is no pharmacopoeial monograph for nicotine lozenges.

The finished product specification is satisfactory. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

CONTAINER-CLOSURE SYSTEM

Clear, Colourless Laminate comprising: 76 micron UltRx3000 ACLAR / Adhesive / 254 micron PVC blister pack comprising of 20 micron Aluminium Foil with heat seal lacquer; 21 shelf life when stored below 25ºC and in the original container.

Clear, Colourless Laminate comprising: 60 micron PVC/240 micron COC (Cyclic Olefin Copolymer) / 90gsm PVdC blister pack comprising of 20 micron Aluminium Foil with heat seal lacquer; 18 shelf life when stored below 25ºC and in the original container.

Clear, Colourless Triplex Laminate comprising: 250 ±5% µm Clear UPVC/25 – 35 µm Low density Polyethylene/90 ±5% gm^{-2} PVdC Coating blister pack comprising of 20 micron Aluminium Foil with heat seal lacquer; 18 shelf life when stored below 25ºC and in the original container.

Specifications and certificates of analysis for the primary packaging material have been provided. These are satisfactory.

STABILITY

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 9 months with the storage conditions “Do not store above 25 °C” has been proposed and is acceptable.

Suitable post-approval have been made for continued testing of the product.

MODULE 1

MAA Form

The MAA form is acceptable

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is acceptable

LABELLING

The labels are acceptable

PATIENT INFORMATION LEAFLET (PIL)

There are no pharmaceutical issues with the PIL.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION AND BACKGROUND

These national complex abridged applications are for sublingual tablets containing 2 mg and 4 mg of Nicotine in the form of nicotine resinate. These applications have been made under a last paragraph generic application under Article 10.1(a)(iii) of Directive 2001/83/EC, as amended. These applications are supported with a dossier including administrative, quality, pre-clinical and clinical bioequivalence data.

It is an abridged application relying on the clinical data of the reference product, NiQuitin CQ 4mg Lozenge. This is appropriate in the case of a generic product. 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 and none are provided by the applicant.

Nicotine is a liquid alkaloid obtained from the dried leaves of the tobacco plant, Nicotiana tabacum and related species (Solanaceae). Tobacco leaves contain 0.5 to 8% of nicotine combined as malate or citrate.

Nicotine is readily absorbed through mucous membranes and the skin; bioavailability of oral nicotine is low due to extensive first pass metabolism. Nicotine is widely distributed; it crosses the blood brain barrier and the placenta and is found in breast milk. The elimination half life is about 1 to 2 hours. Nicotine is metabolised mainly in the liver via the cytochrome P450 isoenzyme CYP2A6 to cotine and nicotine-N-oxide. Nicotine and its metabolites are excreted in the urine.

2. INDICATIONS

The applicant has submitted the following:

Nicotine 4 mg Lozenges are indicated for the relief of nicotine withdrawal symptoms including cravings associated with smoking cessation. Nicotine 4 mg Lozenges should preferably be used in conjunction with a behavioural support programme.

This is identical to the indications of the UK reference product and therefore satisfactory.

3. DOSE & DOSE SCHEDULE

The proposed posology is consistent with that detailed in section 4.2 of the SPC of the originator product:

> Adults (including the elderly):
>
> Nicotine 4 mg Lozenges are suitable for smokers who have their first cigarette of the day within 30 minutes of waking up.
> Users should stop smoking completely during treatment with Nicotine 4 mg Lozenges.

Users should follow the schedule of treatment below:

Step 1 Weeks 1 to 6	Step 2 Weeks 7 to 9	Step 3 Weeks 10 to 12	To help stay smoke free over the next 12 weeks: use 1-2 lozenges per day only on occasions when strongly tempted to smoke
Initial treatment period	Step down treatment period	Step down treatment period	
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours	

During weeks 1 to 6 it is recommended that users take a minimum of 9 lozenges per day.
Users should not exceed 15 lozenges per day.
Lozenges should not be used for more than 24 weeks (6 months). If users still feel the need for treatment, a physician should be consulted.

Directions for Use

One lozenge should be placed in the mouth and allowed to dissolve. Periodically, the lozenge should be moved from one side of the mouth to the other, and repeated, until the lozenge is completely dissolved (approximately 20 – 30 minutes). The lozenge should not be chewed or swallowed whole.
Users should not eat or drink while a lozenge is in the mouth.

Children and adolescents

Safety and effectiveness in children and adolescents who smoke have not been evaluated. Nicotine 4 mg Lozenges are not recommended for use in children and adolescents under the age of 18.

4. CLINICAL PHARMACOLOGY

To support the application, the applicant has submitted a single bioavailability study: a single centre, single-blind, single dose, randomised, two period cross – over trial comparing Nicotine Lozenge 4mg with the reference NiQuitin CQ 4mg Lozenge in healthy smokers.

Study protocol
27 healthy 15-25/day smokers, 17 male and 10 female, aged 18-31 years, were included in this study. Three subjects were 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: NiQuitin Lozenge 4mg

Test: Nicotine Lozenge 4mg

The reference is registered in UK. The tablets were given following a controlled period of fasting. Subjects were free to eat from 4.5 h post-dose. Blood samples were taken at pre-dose and at 10, 20, 30, 45mins and 1, 1.25, 1.5, 2, 3, 4, 6, 9 and 12 hours after administration of the products.

Plasma samples were analysed for nicotine by LC-MS/MS. The limit of quantification was 0.5ng/ml. The method was validated and the validation report was provided.

AUC (0-t.), AUC (0-inf), Cmax, tmax and t½ were calculated according normal standard procedures.

Statistical evaluation was performed for AUC (0-t), AUCinf and Cmax with ANOVA and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated.

Table 8: Point Estimates, Confidence Intervals and CVs for primary parameters A vs B

	C_{max} (ng/mL)	AUC_{0-t} (ng/mL.h)
Point Estimate	90.54	97.30
90% CI	84.04%-97.54%	92.23%-102.64%
Intra-subject CV	15.11	10.82
Inter-subject CV	19.33	35.51

Table 9: Point Estimates, Confidence Intervals and CVs for additional parameters A vs B

	$AUC_{0-\infty}$	C_{max}/ $AUC_{0-\infty}$	$t_{1/2}$ (h)	MRT (h)	t_{max} (h)
Point Estimate	96.97	93.37	95.73	102.27	0.2500
90% CI	91.28%-103.02%	85.89%-101.50%	86.28%-106.22%	94.84%-110.28%	0.040-0.415
Intra-subject CV	12.25	16.96	21.21	15.31	NC
Inter-subject CV	34.10	16.43	21.74	16.45	NC

NC = Not Calculated

The claim that bioequivalence has been demonstrated is endorsed.

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

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

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

8. PATIENT INFORMATION LEAFLET (PIL)
The PIL properly reflects the SPC.

9. LABELLING
The labelling text is medically satisfactory.

10. APPLICATION FORM (MAA)
The MAA is medically satisfactory.

11. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
The SPC is consistent with that licensed for the UK reference product and is satisfactory.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Asda / NicAid / Morrison's / Superdrug / Sainsbury's / Wilko / Paramed Nicotine 2mg and 4mg Lozenges are well-defined and controlled. 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

To support the application, the applicant has submitted a single bioavailability study. The claim that bioequivalence has been demonstrated is endorsed. No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant's product and the innovator product are interchangeable. Clinical experience with this product is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

ASDA / NICAID / MORRISON'S / SUPERDRUG / SAINSBURY'S / WILKO / PARAMED NICOTINE 2MG AND 4MG LOZENGES PL 12063/0068-69

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 17/03/2005
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 23/03/2005.
3	Following assessment of the application the MHRA requested further information relating to the dossier on 02/12/2005, 14/02/2006, 17/08/2006, 19/06/2006
4	The applicant responded to the MHRA's requests, providing further information relating to the quality dossier on 19/06/2006, 21/10/2006
5	The application was determined on 26/02/2007.

ASDA / NICAID / MORRISON'S / SUPERDRUG / SAINSBURY'S / WILKO / PARAMED NICOTINE 2MG AND 4MG LOZENGES PL 12063/0068-69

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

ASDA / NICAID / MORRISON'S / SUPERDRUG / SAINSBURY'S / WILKO / PARAMED NICOTINE 2MG AND 4MG LOZENGES PL 12063/0068-69

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Paramed Nicotine 2 mg Lozenges
Wilko Nicotine 2 mg Lozenges
NicAid 2 mg Lozenges
Sainsbury's Nicotine 2 mg Lozenges
Superdrug Nicotine 2 mg Lozenges
ASDA Nicotine 2 mg Lozenges
Morrison's Nicotine 2 mg Lozenges

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each lozenge contains 2 mg nicotine (as 13.33 mg Nicotine Resinate)
For full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Compressed lozenge
Cream/white, biconvex round lozenge, embossed 'L344'

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nicotine 2 mg Lozenges are indicated for the relief of nicotine withdrawal symptoms including cravings associated with smoking cessation. Nicotine 2 mg Lozenges should preferably be used in conjunction with a behavioural support programme.

4.2 Posology and method of administration

Adults (including the elderly):
Nicotine 2 mg Lozenges are suitable for smokers who have their first cigarette of the day more than 30 minutes after waking up.
Users should make every effort to stop smoking completely during treatment with Nicotine 2 mg Lozenges.

The suggested treatment is:

Step 1 Weeks 1 to 6	Step 2 Weeks 7 to 9	Step 3 Weeks 10 to 12	To help stay smoke free over the next 12 weeks: use 1-2 lozenges per day only on occasions when strongly tempted to smoke
Initial treatment period	Step down treatment period	Step down treatment period	
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours	

During weeks 1 to 6 it is recommended that users take a minimum of 9 lozenges per day.
Users should not exceed 15 lozenges per day.

Adults who require Nicotine Replacement Therapy (NRT) beyond 9 months should seek additional help and advice from a healthcare professional.

Directions for use
One lozenge should be placed in the mouth and allowed to dissolve. Periodically, the lozenge should be moved from one side of the mouth to the other, and repeated, until the lozenge is completely dissolved (approximately 20 – 30 minutes). The lozenge should not be chewed or swallowed whole.

Users should not eat or drink while a lozenge is in the mouth.
Children and adolescents
Safety and effectiveness in children and adolescents who smoke have not been evaluated. Nicotine 2 mg Lozenges are not recommended for use in children under the age of 12.

Adolescents (12-17 years) should follow the schedule of treatment for adults in the table above for step 1, 2 and 3, but as data are limited, duration of NRT in this age group is restricted to 12 weeks. If longer treatment is required advice from a healthcare professional should be sought.

4.3 Contraindications

Nicotine 2 mg Lozenges are contraindicated in:
• hypersensitivity to nicotine or any of the excipients
• children under the age of 12 years and non smokers

4.4 Special warnings and precautions for use

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

Patients hospitalized for MI, severe dysrhythmia or CVA who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions. If this fails, Nicotine 2 mg Lozenges may be considered, but as data on safety in this patient group are limited, initiation should only be under medical supervision. Once patients are discharged from hospital they can use NRT as normal.

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

Allergic reactions: Susceptibility to angioedema and urticaria
A risk benefit assessment should be made by an appropriate healthcare professional for patients with the following conditions:

•*Renal and hepatic impairment*: Use with caution in patients with moderate to severe hepatic impairment and/or severe renal impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse events
•*Phaeochromocytoma and uncontrolled hyperthyroidism:* Use with caution in patients with uncontrolled hyperthyroidism or phaeochromocytoma as nicotine causes release of catecholamines.

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

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

Stopping smoking: Polycyclic aromatic hydrocarbons in tobacco smoke induce the metabolism of drugs catalysed by CYP 1A2 (and possibly by CYP 1A1). When a smoker stops this may result in a slower metabolism and a consequent rise in blood levels of such drugs.

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

Phenylketonuria: Nicotine 2 mg Lozenges are sugar free, but do contain aspartame which metabolises to phenylalanine, which is of relevance for those with phenylketonuria.

Sodium content: Each Nicotine 2 mg Lozenge contains 15 mg of sodium. People on a low sodium diet should take this into account.

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.

4.6 Pregnancy and lactation

Pregnancy
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. 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.

However, as nicotine passes to the foetus affecting breathing movements and has a dose dependent effect on placental/foetal circulation, the decision to use NRT should be made as early on in the pregnancy as possible. The aim should be to use NRT for only 2-3 months.
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 to.
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

Not applicable.

4.8 Undesirable effects

NRT can cause adverse reactions similar to those associated with nicotine administered in other way, including smoking. These may be attributed to the pharmacological effects of nicotine, which are dose dependent. At recommended doses Nicotine 2 mg Lozenges have not been found to cause any serious adverse effects. Excessive consumption of Nicotine 2 mg Lozenges by those who have not been in the habit of inhaling tobacco smoke could possibly lead to nausea, faintness or headaches.

Certain symptoms which have been reported such as depression, irritability, anxiety and

insomnia may be related to withdrawal symptoms associated with smoking cessation. Subjects quitting smoking by any means could expect to suffer from headache, dizziness, sleep disturbance, increased coughing or a cold.

Related adverse events with excess in active compared to placebo group in a controlled study.

Probability of an adverse reaction:

Very common
Gastrointestinal system disorders Very common >1/10: nausea; hiccup, flatulence.

Common
Psychiatric disordersCommon >1/100; <1/10: insomnia.
Central and peripheral nervous system disorders Common >1/100; <1/10: dizziness; headache.

Respiratory system disorders Common >1/100; <1/10: coughing; pharyngitis; sore throat.
Common >1/100; <1/10: vomiting; constipation, diarrheoa; dysphagia; dyspepsia; heartburn; indigestion; belching; mouth irritation, mouth ulceration; tongue ulceration; dry mouth; bloating.

Uncommon
Platelet, bleeding and clotting disorders Uncommon >1/1000; <1/100: gingival bleeding

Metabolic and nutritional disorders.

Uncommon >1/1000; <1/100: thirst; excessive thirst.

Uncommon >1/1000; <1/100: anxiety; anxiety attack; anxiety reaction; nightmares; marked restlessness; decreased appetite; lost appetite; lethargy.

Uncommon >1/1000; <1/100; migraine*;* mucosal burning; burning sensation; paraesthesia mouth; sensory disturbance; hyperalertness.

Uncommon >1/1000; <1/100: dyspnoea; shortness of breath; aggravated cough; lower respiratory tract infection; respiratory disorder; excessive sneezing.

Uncommon >1/1000; <1/100: gastroesophageal reflux; oesophageal reflux aggravated; retching; eructation; gagging; catarrh; increased saliva; lip ulceration; GI disorder; abdominal griping; sore lips; dry throat.
Special senses other, disorders: Uncommon >1/1000; <1/100: taste perversion.
Skin and appendages disorders: Uncommon >1/1000; <1/100: itching; rash Body as a whole: general disorders.

Uncommon >1/1000; <1/100: throat swelling; chest pain; tightness of chest; overdose effect; withdrawal syndrome; malaise; hot flushes; halitosis.

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

ATC Code NO 7B A01

Nicotine is an agonist at nicotine receptors in the peripheral and central nervous system and has pronounced CNS and cardiovascular effects. When consumed in tobacco products, it has been shown to be addictive and abstinence is linked to craving and withdrawal symptoms. These craving and withdrawal symptoms include urge to smoke, depressed mood, insomnia, irritability, frustration or anger, anxiety, difficulty in concentrating, restlessness and increased appetite or weight gain. The lozenges replace some of the nicotine provided by tobacco and help reduce the severity of these nicotine craving and withdrawal symptoms.

5.2 Pharmacokinetic properties

Nicotine 2 mg Lozenges completely dissolve in the oral cavity, and the entire amount of nicotine contained in the lozenge becomes available for buccal absorption or ingestion (swallowing). The complete dissolution of Nicotine 2 mg Lozenge is typically achieved in 20-30 minutes. The peak plasma concentrations of nicotine achieved after a single dose are approximately 4.4 ng/ml. When dosed every 1.5 hours, the steady state peak and trough concentrations are 12.7 and 9.4 ng/ml respectively. Ingestion of Nicotine 2 mg Lozenges not following dosing instructions (chewed, retained in the mouth, and swallowed; chewed and immediately swallowed) does not result in faster or higher absorption, but a substantial amount of nicotine (80-93%) is still absorbed.

As the plasma protein binding of nicotine is low (4.9% - 20%), the volume of distribution of nicotine is large (2.5 l/kg). The distribution of nicotine to tissue is pH dependent, with the highest concentrations of nicotine found in the brain, stomach, kidney and liver.

Nicotine is extensively metabolized to a number of metabolites, all of which are less active than the parent compound. The metabolism of nicotine primarily occurs in the liver, but also in the lung and kidney. Nicotine is metabolized primarily to cotinine but is also metabolized to nicotine N′-oxide. Cotinine has a half-life of 15-20 hours and its blood levels are 10 times higher than nicotine. Cotinine is further oxidized to *trans*-3′-hydroxycotinine, which is the most abundant metabolite of nicotine in the urine. Both nicotine and cotinine undergo glucuronidation.

The elimination half-life of nicotine is approximately 2 hours (range 1 - 4 hours). Total clearance for nicotine ranges from approximately 62 to 89 l/hr. Non-renal clearance for nicotine is estimated to be about 75% of total clearance. Nicotine and its metabolites are excreted almost exclusively in the urine. The renal excretion of unchanged nicotine is highly dependent on urinary pH, with greater excretion occurring at acidic pH.

5.3 Preclinical safety data

The general toxicity of nicotine is well known and taken into account in the recommended posology. Nicotine was not mutagenic in appropriate assays. The results of carcinogenicity assays did not provide any clear evidence of a tumorigenic effect of nicotine. In studies in pregnant animals, nicotine showed maternal toxicity, and consequential mild foetal toxicity. Additional effects included pre- and postnatal growth retardation and delays and changes in postnatal CNS development.

Effects were only noted following exposure to nicotine at levels in excess of those which will result from recommended use of Nicotine 2 mg Lozenges. Effects on fertility have not been established.

Comparison of the systemic exposure necessary to elicit these adverse responses from preclinical test systems with that associated with the recommended use of Nicotine 2 mg Lozenges indicate that the potential risk is low and outweighed by the demonstrable benefit of nicotine therapy in smoking cessation. However, Nicotine 2 mg Lozenges should only be used by pregnant women on medical advice if other forms of treatment have failed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Magnesium stearate
Sodium alginate
Xanthan gum
Potassium bicarbonate
Sodium carbonate anhydrous
Aspartame
Peppermint flavour

6.2 Incompatibilities

Not applicable

6.3 Shelf life

21 months in ACLAR/PVC/AL blisters
18 months in COC/PVdC/AL and uPVC/PVdC/AL blisters

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Clear, Colourless Laminate comprising: 76 micron UltRx3000 ACLAR / Adhesive / 254 micron PVC blister pack comprising of 20 micron Aluminium Foil with heat seal lacquer.

Clear, Colourless Laminate comprising: 60 micron PVC/240 micron COC (Cyclic Olefin Copolymer) / 90gsm PVdC blister pack comprising of 20 micron Aluminium Foil with heat seal lacquer.

Clear, Colourless Triplex Laminate comprising: 250 ±5% µm Clear UPVC/25 – 35 µm Low density Polyethylene/90 ±5% gm^{-2} PVdC Coating blister pack comprising of 20 micron Aluminium Foil with heat seal lacquer.

Each pack contains 36 or 72 lozenges in a cardboard carton.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Wrafton Laboratories Limited
Wrafton
Braunton
Devon
EX33 2DL

8 MARKETING AUTHORISATION NUMBER(S)

PL 12063/0068

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/02/2007

10 DATE OF REVISION OF THE TEXT

26/02/2007

1 NAME OF THE MEDICINAL PRODUCT

Paramed Nicotine 4 mg Lozenges
Wilko Nicotine 4 mg Lozenges
NicAid 4 mg Lozenges
Sainsbury's 4mg Nicotine Lozenges
Superdrug Nicotine 4 mg Lozenges
ASDA Nicotine 4 mg Lozenges
Morrison's Nicotine 4 mg Lozenges

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each lozenge contains 4 mg nicotine (as 26.660 mg nicotine resinate)

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Compressed lozenge
Cream/white, biconvex round lozenge, embossed with 'L873'

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nicotine 4 mg Lozenges are indicated for the relief of nicotine withdrawal symptoms including cravings associated with smoking cessation. Nicotine 4 mg Lozenges should preferably be used in conjunction with a behavioural support programme.

4.2 Posology and method of administration

Adults (including the elderly):
Nicotine 4 mg Lozenges are suitable for smokers who have their first cigarette of the day within 30 minutes of waking up.

Users should make every effort to stop smoking completely during treatment with Nicotine 4 mg Lozenges.

The suggested treatment is:

Step 1 **Weeks 1 to 6**	**Step 2** **Weeks 7 to 9**	**Step 3** **Weeks 10 to 12**	To help stay smoke free over the next 12 weeks: use 1-2 lozenges per day only on occasions when strongly tempted to smoke
Initial treatment period	Step down treatment period	Step down treatment period	
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours	

During weeks 1 to 6 it is recommended that users take a minimum of 9 lozenges per day.
Users should not exceed 15 lozenges per day.
Adults who require Nicotine Replacement Therapy (NRT) beyond 9 months should seek additional help and advice from a healthcare professional.

Directions for Use
One lozenge should be placed in the mouth and allowed to dissolve. Periodically, the lozenge should be moved from one side of the mouth to the other, and repeated, until the lozenge is completely dissolved (approximately 20 – 30 minutes). The lozenge should not be chewed or swallowed whole.

Users should not eat or drink while a lozenge is in the mouth.

Children and Adolescents
Safety and effectiveness in children and adolescents who smoke have not been evaluated. Nicotine 4 mg Lozenges are not recommended for use in children under the age of 12.
Adolescents (12-17 years) should follow the schedule of treatment for adults in the table above for step 1, 2 and 3, but as data are limited, duration of NRT in this age group is restricted to 12 weeks. If longer treatment is required advice from a healthcare professional should be sought.

4.3 Contraindications

Nicotine 4 mg Lozenges are contraindicated in:
• hypersensitivity to nicotine or any of the excipients
• children under the age of 12 years and non smokers

4.4 Special warnings and precautions for use

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

Patients hospitalized for MI, severe dysrhythmia or CVA who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions. If this fails,Nicotine 4 mg Lozenges may be considered, but as data on safety in this patient group are limited, initiation should only be under medical supervision. Once patients are discharged from hospital they can use NRT as normal.

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

Allergic reactions: Susceptibility to angioedema and urticaria
A risk benefit assessment should be made by an appropriate healthcare professional for patients with the following conditions:

•*Renal and hepatic impairment*: Use with caution in patients with moderate to severe hepatic impairment and/or severe renal impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse events
•*Phaeochromocytoma and uncontrolled hyperthyroidism:* Use with caution in patients with uncontrolled hyperthyroidism or phaeochromocytoma as nicotine causes release of catecholamines.

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

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

Stopping smoking: Polycyclic aromatic hydrocarbons in tobacco smoke induce the metabolism of drugs catalysed by CYP 1A2 (and possibly by CYP 1A1). When a smoker stops this may result in a slower metabolism and a consequent rise in blood levels of such drugs.

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

*Phenylketonuria:*Nicotine 4 mg Lozenges are sugar free, but do contain aspartame which metabolises to phenylalanine, which is of relevance for those with phenylketonuria.

Sodium content: EachNicotine 4 mg Lozenge contains 15 mg of sodium. People on a low sodium diet should take this into account.

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.

4.6 Pregnancy and lactation

Pregnancy

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. 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.

However, as nicotine passes to the foetus affecting breathing movements and has a dose dependent effect on placental/foetal circulation, the decision to use NRT should be made as early on in the pregnancy as possible. The aim should be to use NRT for only 2-3 months.
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 to.

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

Not applicable.

4.8 Undesirable effects

NRT can cause adverse reactions similar to those associated with nicotine administered in other way, including smoking. These may be attributed to the pharmacological effects of nicotine, which are dose dependent. At recommended doses Nicotine 4 mg Lozenges have not been found to cause any serious adverse effects. Excessive consumption of Nicotine 4 mg Lozenges by those who have not been in the habit of inhaling tobacco smoke could possibly lead to nausea, faintness or headaches.

Certain symptoms which have been reported such as depression, irritability, anxiety and insomnia may be related to withdrawal symptoms associated with smoking cessation. Subjects quitting smoking by any means could expect to suffer from headache, dizziness, sleep disturbance, increased coughing or a cold.

Related adverse events with excess in active compared to placebo group in a controlled study.
Probability of an adverse reaction:

Very common
Gastrointestinal system disorders Very common >1/10: nausea; hiccup, flatulence.

Common
Psychiatric disordersCommon >1/100; <1/10: insomnia.
Central and peripheral nervous system disorders Common >1/100; <1/10: dizziness; headache.

Respiratory system disorders Common >1/100; <1/10: coughing; pharyngitis; sore throat.
Common >1/100; <1/10: vomiting; constipation, diarrheoa; dysphagia; dyspepsia; heartburn; indigestion; belching; mouth irritation, mouth ulceration; tongue ulceration; dry mouth; bloating.

Uncommon
Platelet, bleeding and clotting disorders Uncommon >1/1000; <1/100: gingival bleeding
Metabolic and nutritional disorders.

Uncommon >1/1000; <1/100: thirst; excessive thirst.

Uncommon >1/1000; <1/100: anxiety; anxiety attack; anxiety reaction; nightmares; marked restlessness; decreased appetite; lost appetite; lethargy.

Uncommon >1/1000; <1/100; migraine*;* mucosal burning; burning sensation; paraesthesia mouth; sensory disturbance; hyperalertness.

Uncommon >1/1000; <1/100: dyspnoea; shortness of breath; aggravated cough; lower respiratory tract infection; respiratory disorder; excessive sneezing.
Uncommon >1/1000; <1/100: gastroesophageal reflux; oesophageal reflux aggravated; retching; eructation; gagging; catarrh; increased saliva; lip ulceration; GI disorder; abdominal griping; sore lips; dry throat.

Special senses other, disorders: Uncommon >1/1000; <1/100: taste perversion.
Skin and appendages disorders: Uncommon >1/1000; <1/100: itching; rash Body as a whole: general disorders.

Uncommon >1/1000; <1/100: throat swelling; chest pain; tightness of chest; overdose effect; withdrawal syndrome; malaise; hot flushes; halitosis.

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
ATC Code NO 7B A01

Nicotine is an agonist at nicotine receptors in the peripheral and central nervous system and has pronounced CNS and cardiovascular effects. When consumed in tobacco products, it has been shown to be addictive and abstinence is linked to craving and withdrawal symptoms. These craving

and withdrawal symptoms include urge to smoke, depressed mood, insomnia, irritability, frustration or anger, anxiety, difficulty in concentrating, restlessness and increased appetite or weight gain. The lozenges replace some of the nicotine provided by tobacco and help reduce the severity of these nicotine craving and withdrawal symptoms.

5.2 Pharmacokinetic properties

Nicotine 4 mg Lozenges completely dissolve in the oral cavity, and the entire amount of nicotine contained in the lozenge becomes available for buccal absorption or ingestion (swallowing). The complete dissolution of Nicotine 4mg Lozenge is typically achieved in 20-30 minutes. The peak plasma concentrations of nicotine achieved after a single dose are approximately 4.4 ng/ml. When dosed every 1.5 hours, the steady state peak and trough concentrations are 26.0 and 19.7 ng/ml respectively. Ingestion of Nicotine 4 mg Lozenges not following dosing instructions (chewed, retained in the mouth, and swallowed; chewed and immediately swallowed) does not result in faster or higher absorption, but a substantial amount of nicotine (80-93%) is still absorbed.

As the plasma protein binding of nicotine is low (4.9% - 20%), the volume of distribution of nicotine is large (2.5 l/kg). The distribution of nicotine to tissue is pH dependent, with the highest concentrations of nicotine found in the brain, stomach, kidney and liver.
Nicotine is extensively metabolized to a number of metabolites, all of which are less active than the parent compound. The metabolism of nicotine primarily occurs in the liver, but also in the lung and kidney. Nicotine is metabolized primarily to cotinine but is also metabolized to nicotine N′-oxide. Cotinine has a half-life of 15-20 hours and its blood levels are 10 times higher than nicotine. Cotinine is further oxidized to *trans*-3′-hydroxycotinine, which is the most abundant metabolite of nicotine in the urine. Both nicotine and cotinine undergo glucuronidation.

The elimination half-life of nicotine is approximately 2 hours (range 1 - 4 hours). Total clearance for nicotine ranges from approximately 62 to 89 l/hr. Non-renal clearance for nicotine is estimated to be about 75% of total clearance. Nicotine and its metabolites are excreted almost exclusively in the urine. The renal excretion of unchanged nicotine is highly dependent on urinary pH, with greater excretion occurring at acidic pH.

5.3 Preclinical safety data

The general toxicity of nicotine is well known and taken into account in the recommended posology. Nicotine was not mutagenic in appropriate assays. The results of carcinogenicity assays did not provide any clear evidence of a tumorigenic effect of nicotine. In studies in pregnant animals, nicotine showed maternal toxicity, and consequential mild fetal toxicity. Additional effects included pre- and postnatal growth retardation and delays and changes in postnatal CNS development.

Effects were only noted following exposure to nicotine at levels in excess of those which will result from recommended use of Nicotine 4 mg Lozenges. Effects on fertility have not been established.

Comparison of the systemic exposure necessary to elicit these adverse responses from preclinical test systems with that associated with the recommended use of Nicotine 4 mg Lozenges indicate that the potential risk is low and outweighed by the demonstrable benefit of nicotine therapy in smoking cessation. However, Nicotine 4 mg Lozenges should only be used by pregnant women on medical advice if other forms of treatment have failed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Magnesium stearate
Sodium alginate
Xanthan gum
Potassium bicarbonate

Sodium carbonate anhydrous
Aspartame
Peppermint flavour

6.2 Incompatibilities
Not applicable

6.3 Shelf life
21 months in ACLAR/PVC/AL blisters
18 months in COC/PVdC/AL and uPVC/PVdC/AL blisters

6.4 Special precautions for storage
Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container
Clear, Colourless Laminate comprising: 76 micron UltRx3000 ACLAR / Adhesive / 254 micron PVC blister pack comprising of 20 micron Aluminium Foil with heat seal lacquer.

Clear, Colourless Laminate comprising: 60 micron PVC/240 micron COC (Cyclic Olefin Copolymer) / 90gsm PVdC blister pack comprising of 20 micron Aluminium Foil with heat seal lacquer.

Clear, Colourless Triplex Laminate comprising: 250 ±5% µm Clear UPVC/25 – 35 µm Low density Polyethylene/90 ±5% gm^{-2} PVdC Coating blister pack comprising of 20 micron Aluminium Foil with heat seal lacquer.

Each pack contains 36 or 72 lozenges in a cardboard carton.

6.6 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORISATION HOLDER
Wrafton Laboratories Limited
Wrafton
Braunton
North Devon
EX33 2DL

8 MARKETING AUTHORISATION NUMBER(S)
PL 12063/0069

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
26/02/2007

10 DATE OF REVISION OF THE TEXT
26/02/2007

ASDA / NICAID / MORRISON'S / SUPERDRUG / SAINSBURY'S / WILKO / PARAMED NICOTINE 2MG AND 4MG LOZENGES PL 12063/0068-69

PATIENT INFORMATION LEAFLET

Patient Information Leaflet

Read all of this leaflet carefully because it contains important information for you. This medicine is available without prescription. You need to use these lozenges carefully to get the best results from them. Keep this leaflet, as you may need to read it again.

1. What are your lozenges made of?

Your cream/white circular compressed lozenge is embossed with L344 and has an odour of peppermint.

The active ingredient is nicotine 2 mg in the form of a resin complex (nicotine resinate 13.33 mg).

Other ingredients are mannitol (E421), magnesium stearate, sodium alginate, xanthan gum, potassium bicarbonate, sodium carbonate anhydrous, aspartame (E951) and peppermint flavour.

Your lozenges are available in pack sizes of 36's and 72's.

2. Who makes your lozenges?

The Marketing Authorisation Holder is Wrafton Laboratories Limited, Wrafton, Braunton, Devon EX33 2DL, UK. Manufactured by Perrigo UK Limited, Swadlincote, Derbyshire DE11 0BB, UK. PL 12063/0068.

3. What are your lozenges used for?

Your lozenges are a stop smoking aid.

They contain a nicotine resin and when sucked, nicotine is released slowly from the resin and absorbed through the lining of the mouth. This nicotine relieves some of the cravings and the unpleasant withdrawal symptoms, such as feeling ill or irritable, that smokers frequently feel when they try to give up.

The nicotine can also reduce your urge to smoke by providing some of the nicotine previously inhaled from cigarettes and helps you resist cigarettes. Because the lozenges do not contain the tar or carbon monoxide of cigarette smoke, they do not have the health dangers of tobacco.

This pack contains lozenges which are for smokers who smoke their first cigarette more than 30 minutes after waking up.

If possible, when giving up smoking these lozenges should be used with a stop smoking behavioural support programme.

4. Before you use these lozenges

Do not use these lozenges if you:

- are allergic to nicotine or any of the ingredients named in section 1
- suffer from phenylketonuria - the lozenges contain a source of phenylalanine, which may be harmful to you
- are a non-smoker.

These lozenges are not for use in children under 12 years.

Seek medical advice before taking these lozenges if you:

- have had a recent heart attack or stroke, or you suffer from severe irregular heartbeat, unstable or worsening angina (chest pain) or resting angina, or have recently come out of hospital - you can use these lozenges to help you stop smoking but should consult your doctor who will advise you if these conditions apply to you and guide you before starting NRT (Nicotine Replacement Therapy)
- have heart or circulation problems including heart failure or stable angina, high blood pressure, or occlusive peripheral artery disease
- have serious liver or kidney disease
- have a stomach ulcer or an over active thyroid gland
- are diabetic, as diabetic patients need to monitor blood sugar levels more closely as nicotine from smoking or NRT may vary them more than usual
- have been diagnosed as having a tumour of the adrenal glands (phaeochromocytoma)
- are pregnant, breastfeeding or planning a pregnancy.

When you stop smoking your metabolism slows down and this may alter the way your body responds to certain medicines.

Note before taking:

Each lozenge contains about 15 mg of sodium and the maximum daily dose of these lozenges (15 lozenges) contains 225 mg sodium. To be taken into consideration if you are on a controlled sodium diet.

Your lozenges are sugar free.

There are no known effects of these lozenges on your ability to drive or use machines. However, you should be aware that giving up smoking can cause behavioural changes that could affect you in this way.

STEP 1	STEP 2	STEP 3
Week 1 to 6	**Week 7 to 9**	**Week 10 to 12**
Initial treatment period	Step down treatment period	Step down treatment period
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

To help you stay smoke free over the next 12 weeks, take a lozenge in situations when you are strongly tempted to smoke.

5. How to use your lozenges

During any attempt to give up smoking using these lozenges, it is important that you stop smoking completely. Smoking even one cigarette decreases your chances of success. These lozenges are suitable for smokers who have their first cigarette of the day more than 30 minutes after waking up and should be used according to the schedule, *above*.

During this initial treatment period (weeks 1 to 6) use at least 9 lozenges a day.

Do not use more than one lozenge at a time and do not use more than 15 lozenges per day.

Lozenges should not be used after 36 weeks (9 months). If you find it difficult to give up these lozenges or if you are worried that you may start smoking again then speak to your doctor or pharmacist.

It is important you complete the step down programme in full. This is because urges to smoke and withdrawal symptoms can occur for weeks after stopping smoking. If you resume smoking you may want to talk to your doctor or pharmacist about how to get the best results from your Superdrug Nicotine 2 mg Lozenges.

6. Dosage

For oral use.

Adults and the elderly: Use the lozenges according to the 3-step schedule, which is designed to gradually reduce the number of lozenges you use.

One lozenge should be placed in the side of the mouth and allowed to dissolve. At intervals, the lozenge should be moved from one side of the mouth to the other; the action should be repeated for 20 to 30 minutes until the lozenge is completely dissolved. The lozenge should not be chewed or swallowed whole.

Adolescents (12 - 17 years): As adult dosage for a 12 week period only.

Not recommended for children under 12 years of age.

Users should not eat or drink while a lozenge is in the mouth as this may reduce the absorption of nicotine.

7. What should you do if you take too many lozenges?

If you take more than the recommended number of lozenges per day, you may suffer a nicotine overdose and need to get advice from your doctor. Signs of overdose include headache, sickness, stomach pains and diarrhoea. In the event that a child has taken any lozenges or if an accidental overdose occurs, contact your doctor or nearest hospital casualty department immediately as this can be fatal. If possible show them the pack or this leaflet.

8. Possible side-effects

Sometimes there can be some minor side-effects from giving up smoking or using the lozenges.

These include:

- sore throat, mouth irritation or difficulty swallowing
- sleep disturbances, dizziness, headache, coughing, anxiety, and irritability
- feeling or being sick, hiccups, belching or wind, abnormal appetite
- diarrhoea, heartburn, indigestion or constipation.

None of the above side-effects are serious, and often wear off after a few days' treatment. Occasionally an increased heart rate may be experienced. If this happens stop using the lozenges and tell your doctor.

Other less common side-effects are:

- nightmares, tiredness, restlessness
- sensory disturbance, breathing problems, worsening asthma, chest pain
- taste disturbance, mouth numbness, bleeding gums, bad breath, thirst
- skin irritation, skin flushes or irritation, nose bleed.

If any of these effects are serious or troublesome and do not improve, or the lozenges upset you in any way, stop using them and tell your doctor or pharmacist.

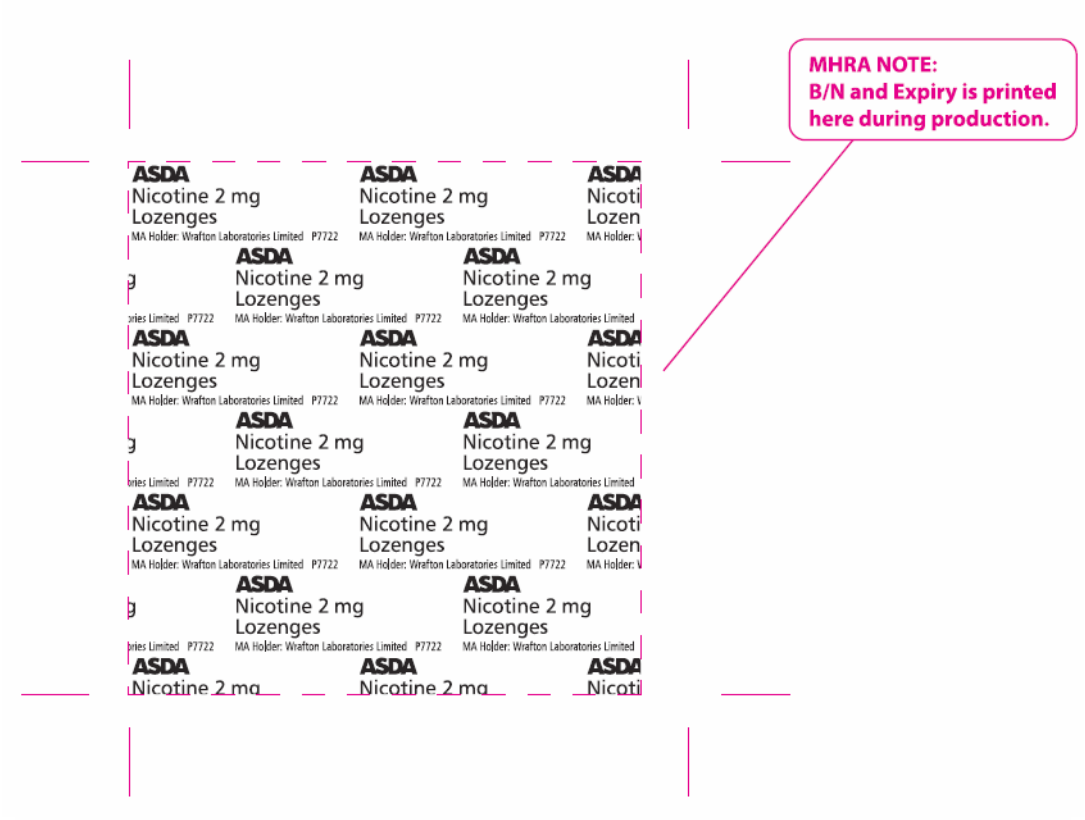
9. Storage precautions

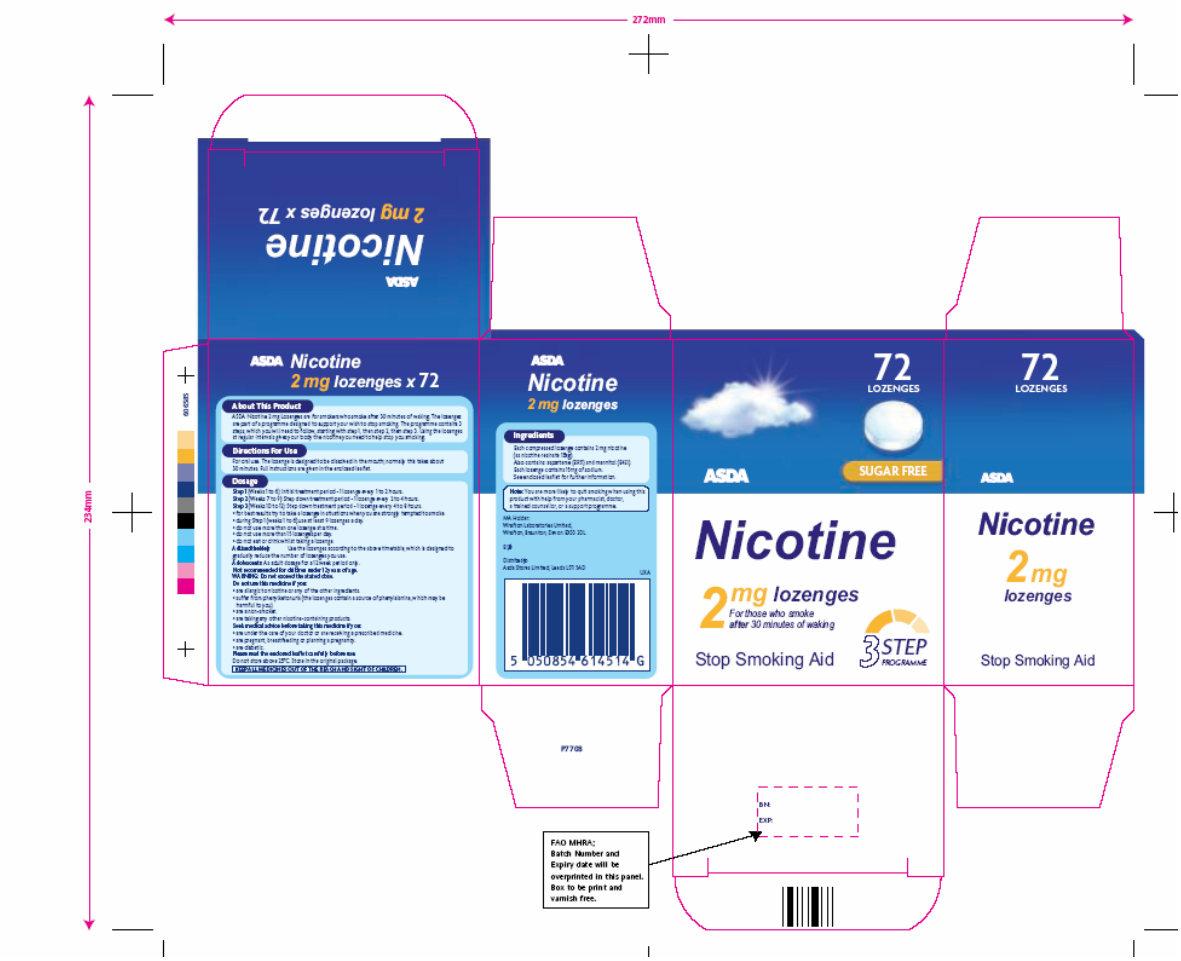
Do not store above 25°C and keep in the original carton. Do not use the lozenges after the expiry date stated on the carton. **Keep all medicines out of the reach and sight of children.**

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

Text Revised: November 2006. P7719

PACKAGING FOR 2MG TABLETS




272mm
234mm
ASDA Nicotine 2 mg lozenges x 72
About This Product
Directions For Use
Dosage
ASDA
Nicotine
2 mg lozenges
Ingredients
72
LOZENGES
SUGAR FREE
Nicotine
2 mg lozenges
For those who smoke after 30 minutes of waking
Stop Smoking Aid
3 STEP PROGRAMME
5 050854 614514 6
FAO MHRA:
Batch Number and Expiry date will be overprinted in this panel. Box to be print and varnish free.

MHRA NOTE:
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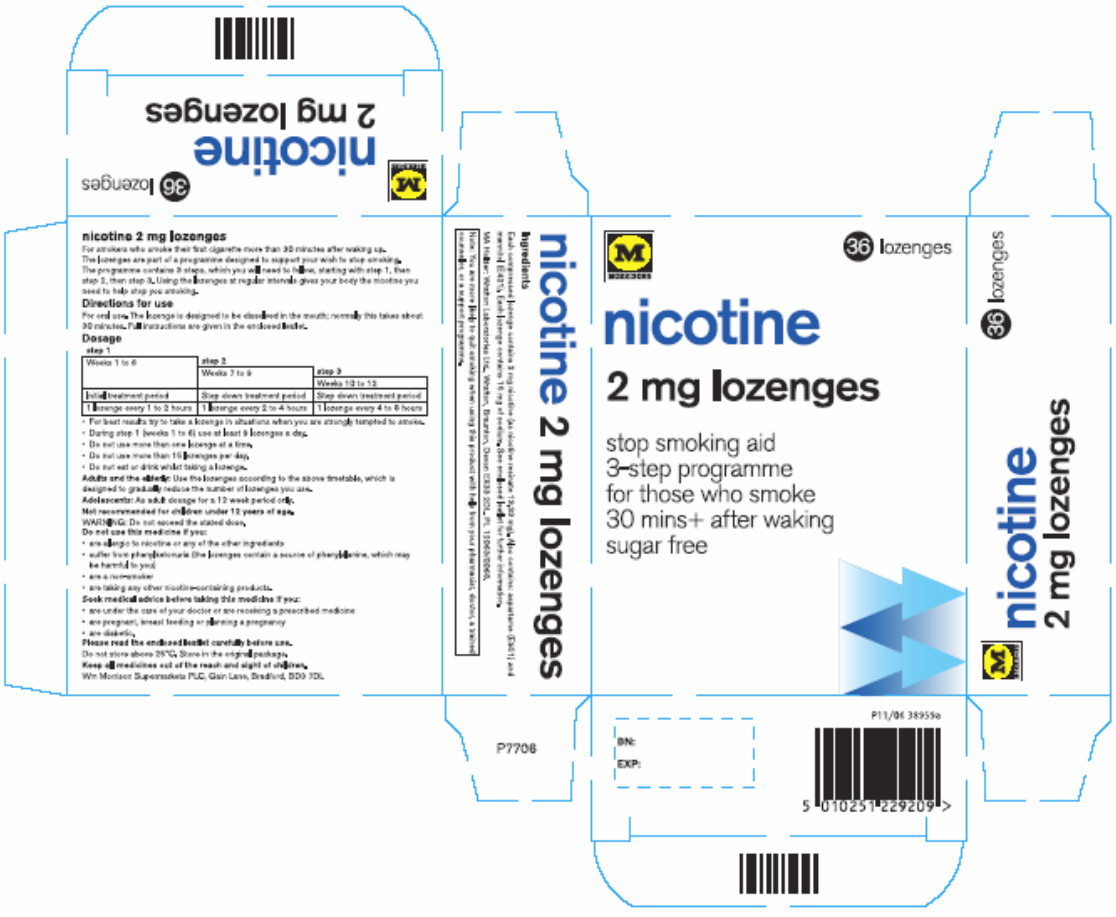

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NICOTINE 2mg LOZENGES
paramed

PARAMED® NICOTINE 2mg LOZENGES

Paramed Nicotine 2mg Lozenges are for smokers who smoke their first cigarette more than 30 minutes after waking up.

The lozenges are part of a programme designed to support your wish to stop smoking. The programme contains 3 steps, which you will need to follow, starting with step 1, then step 2, then step 3. Using the lozenges at regular intervals gives your body the nicotine you need to help stop you smoking.

DIRECTIONS FOR USE

For oral use. The lozenge is designed to be dissolved in the mouth; normally this takes about 30 minutes. Full instructions are given in the enclosed leaflet.

DOSAGE

STEP 1	STEP 2	STEP 3
Week 1 to 6	Week 7 to 9	Week 10 to 12
Initial treatment period.	Step down treatment period.	Step down treatment period.
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

- For best results try to take a lozenge in situations when you are strongly tempted to smoke.
- During Step 1 (weeks 1 to 6) use at least 9 lozenges a day.
- Do not use more than one lozenge at a time.
- Do not use more than 15 lozenges per day.
- Do not eat or drink whilst taking a lozenge.

Adults and the elderly: Use the lozenges according to the above timetable, which is designed to gradually reduce the number of lozenges you use.

Adolescents: As adult dosage for a 12 week period only.

Not recommended for children under 12 years of age.

WARNING: Do not exceed the stated dose.

IMPORTANT

Please read the enclosed leaflet carefully before use

Keep all medicines out of the reach and sight of children

Do not use this medicine if you:
- are allergic to nicotine or any of the other ingredients
- suffer from phenylketonuria (the lozenges contain a source of phenylalanine, which may be harmful to you)
- are a non-smoker
- are taking any other nicotine-containing products.

Seek medical advice before taking this medicine if you:
- are under the care of your doctor or are receiving a prescribed medicine
- are pregnant, breast feeding or planning a pregnancy
- are diabetic.

INGREDIENTS

Each compressed lozenge contains 2 mg nicotine (as nicotine resinate 13.33 mg).
Also contains:
aspartame (E951) and mannitol (E421).
Each lozenge contains 15 mg of sodium.
See enclosed leaflet for further information.

Storage precautions:
Do not store above 25°C.
Store in the original package.

MA Holder:
Wrafton Laboratories Ltd., Wrafton, Braunton, Devon EX33 2DL. PL 12063/0068
'Paramed' is a registered trademark.
© Wrafton Laboratories Limited 2006.

paramed
NICOTINE 2mg LOZENGES 2mg
36 LOZENGES

paramed
NICOTINE 2mg LOZENGES
For those who smoke 30 mins+ after waking
Sugar free
2mg
STOP SMOKING AID
36 LOZENGES
3-STEP PROGRAMME

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

paramed
NICOTINE 2mg LOZENGES 2mg
36 LOZENGES

P7711

BN:
EXP:

5 025331 101306 >

Apart from the pre-printed prefixes, please leave this area free:
NO PRINT NO GRAPHICS NO VARNISH


paramed
NICOTINE
2mg LOZENGES
PARAMED NICOTINE 2mg LOZENGES
IMPORTANT
Please read the enclosed leaflet carefully before use
Keep all medicines out of the reach and sight of children
DIRECTIONS FOR USE
DOSAGE
INGREDIENTS
paramed
NICOTINE
2mg LOZENGES
2mg
72 LOZENGES
For those who smoke 30 mins+ after waking
Sugar free
2mg
STOP SMOKING AID
72 LOZENGES
3-STEP PROGRAMME
You are more likely to quit smoking when using this product with help from your pharmacist, doctor, a trained counsellor, or a support programme.
5 025331 101313
BN:
EXP:
PERRIGO
NICOTINE CARTON
SIZE 76 x 54 x 97 mm
PRINT SIDE
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1st NOV 2006
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MHRA NOTE:
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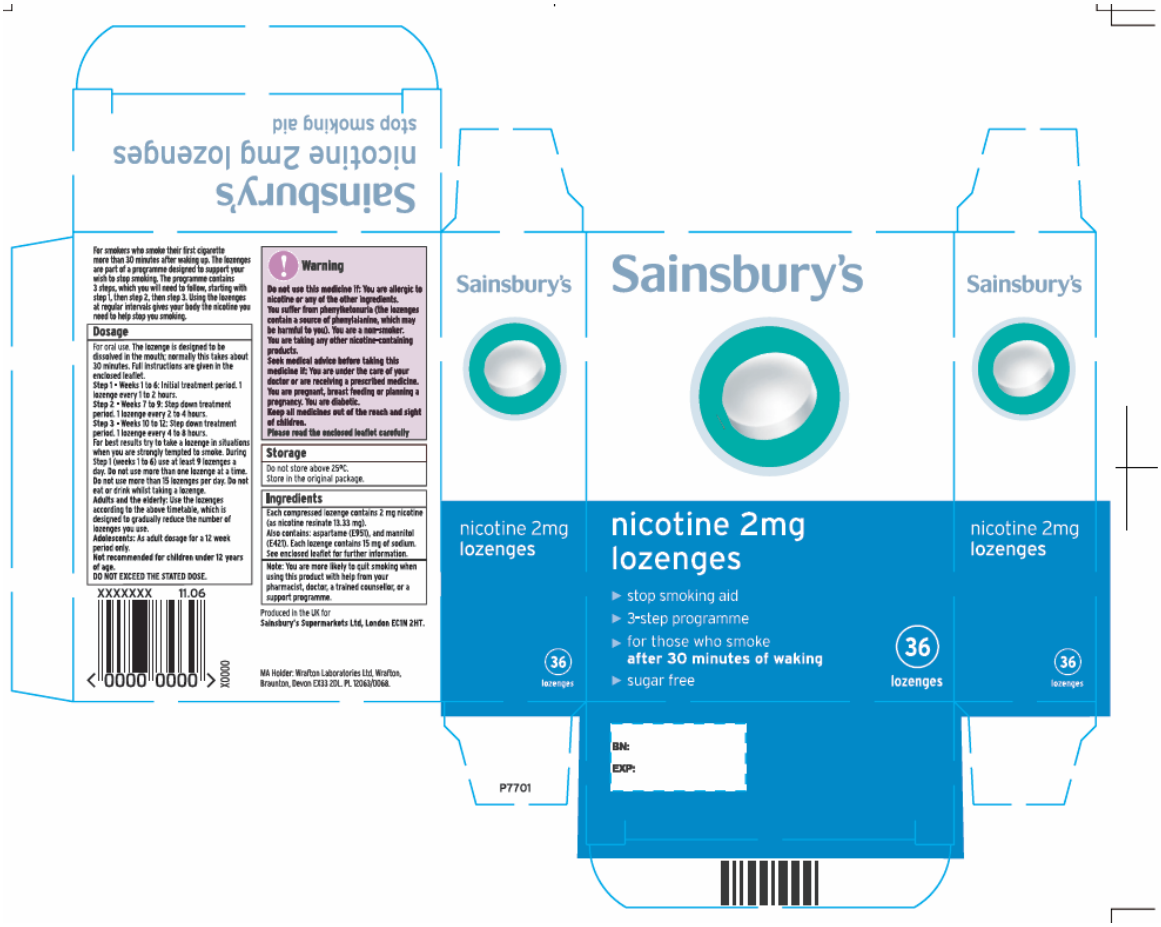
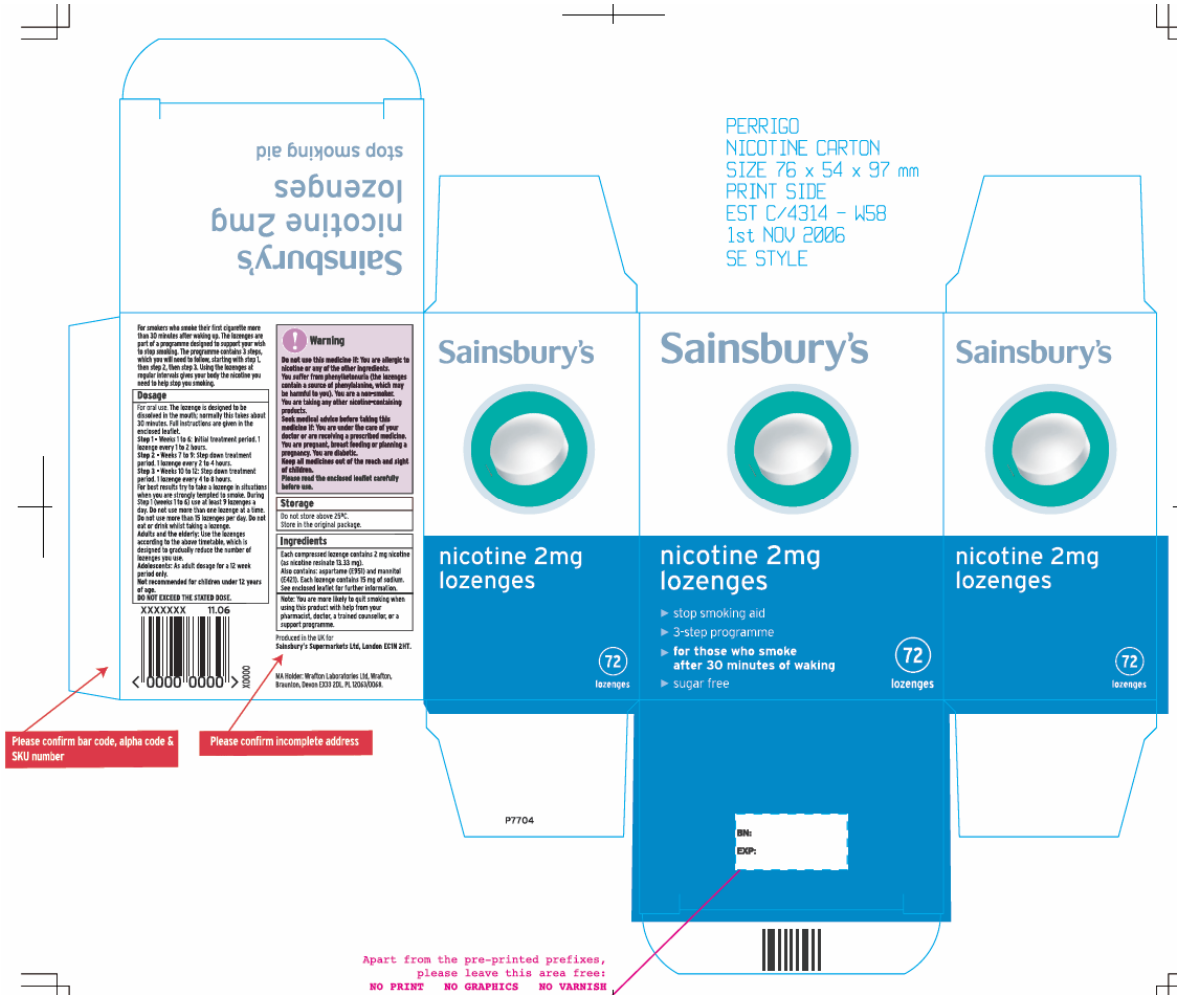
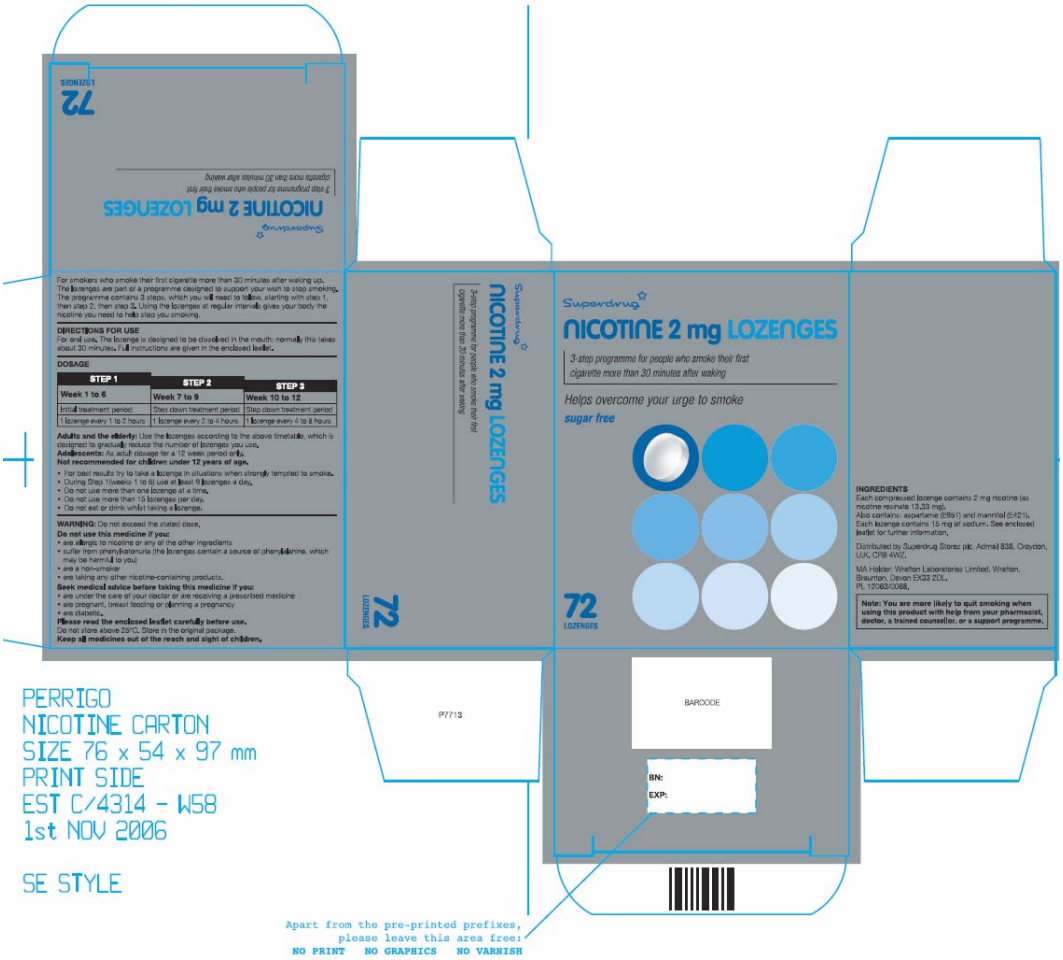



PERRIGO
NICOTINE CARTON
SIZE 76 x 54 x 97 mm
PRINT SIDE
EST C/4314 - W58
1st NOV 2006
SE STYLE
Sainsbury's
nicotine 2mg
lozenges
stop smoking aid
Warning
Dosage
Storage
Ingredients
Produced in the UK for
Sainsbury's Supermarkets Ltd, London EC1N 2HT.
MA Holder: Wrafton Laboratories Ltd, Wrafton,
Braunton, Devon EX33 2DL. PL 12063/0068.
XXXXXXX 11.06
nicotine 2mg lozenges
72 lozenges
stop smoking aid
3-step programme
for those who smoke after 30 minutes of waking
sugar free
P7704
BN:
EXP:
Please confirm bar code, alpha code & SKU number
Please confirm incomplete address
Apart from the pre-printed prefixes, please leave this area free:
NO PRINT NO GRAPHICS NO VARNISH

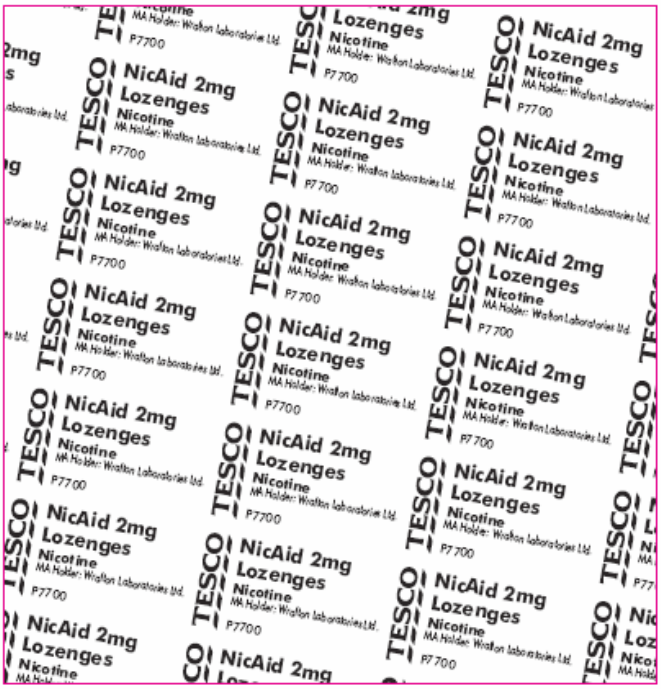
MHRA NOTE:
B/N and Expiry is printed here during production.



PERRIGO
NICOTINE CARTON
SIZE 76 x 54 x 97 mm
PRINT SIDE
EST C/4314 - W58
1st NOV 2006

SE STYLE

Apart from the pre-printed prefixes, please leave this area free
NO PRINT NO GRAPHICS NO VARNISH

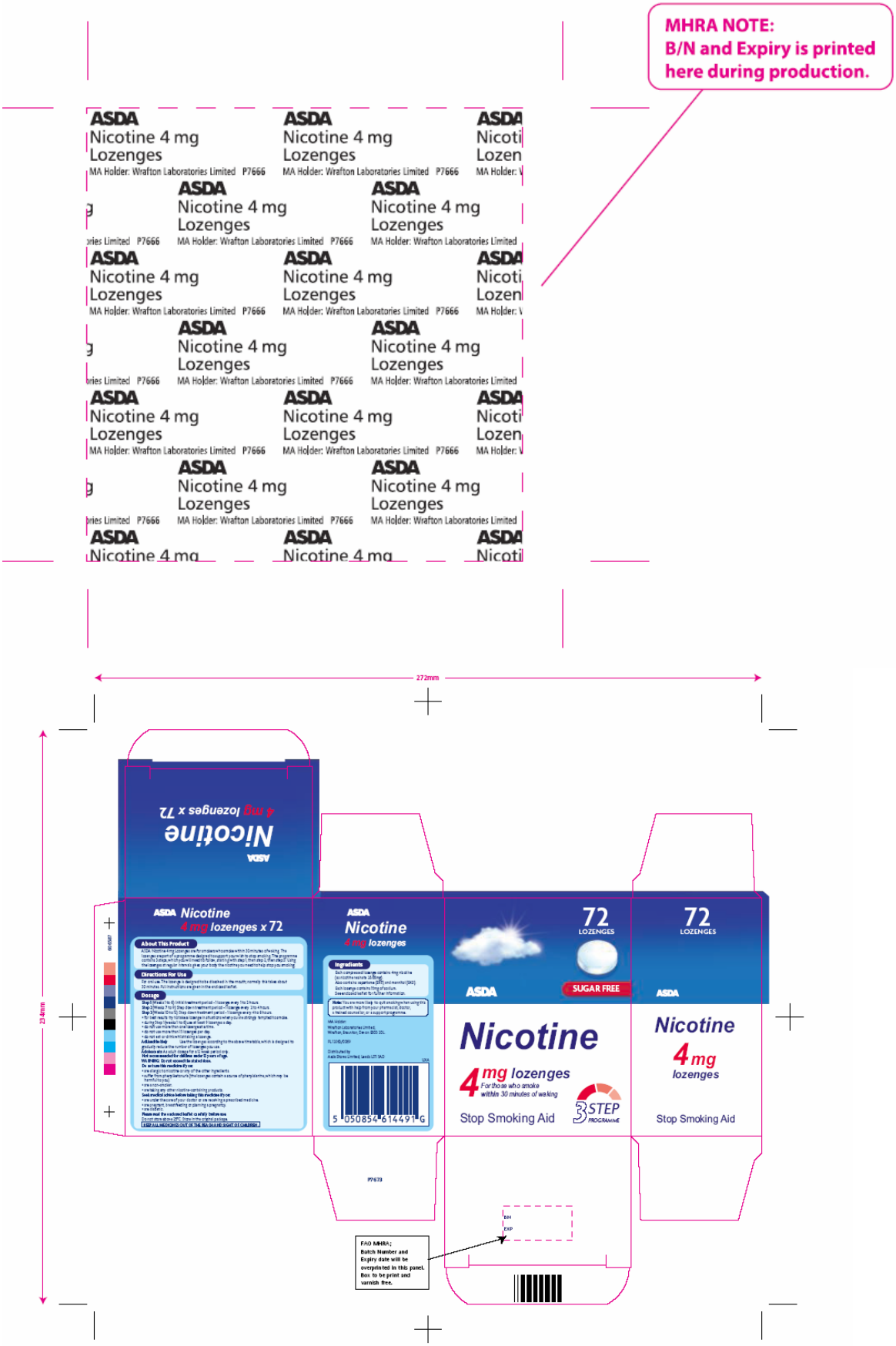

TESCO
NicAid 2mg
Lozenges
Nicotine
MA Holder: Wrafton Laboratories Ltd.
P7700


NicAid
2 mg Lozenges
Nicotine
TESCO
Tesco NicAid 2mg Lozenges
Dosage
Ingredients
Storage
Additional Information
WARNINGS
Do not use
2 mg Lozenges
Nicotine
72 lozenges
2 mg
TESCO
NicAid
2 mg Lozenges
Nicotine
72 lozenges
• For those who smoke 30 mins+ after waking
• Sugar free
P7700
BN:
EXP:

MHRA NOTE:
B/N and Expiry is printed here during production.

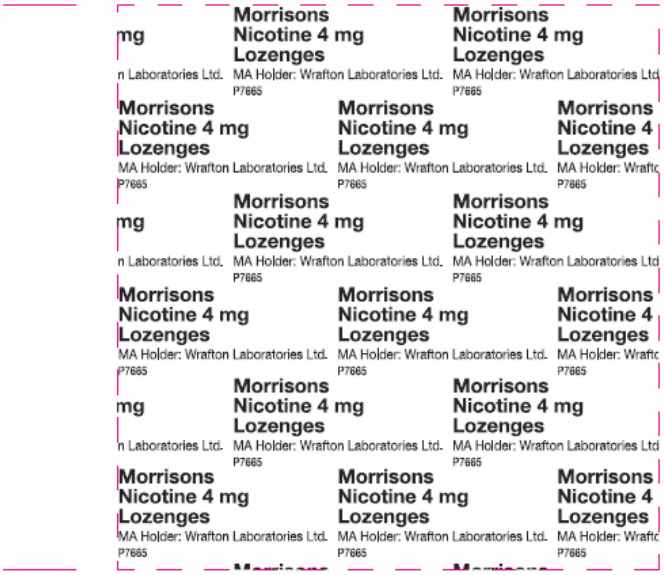
Apart from the pre-printed prefixes, please leave this area free:
NO PRINT NO GRAPHICS NO VARNISH

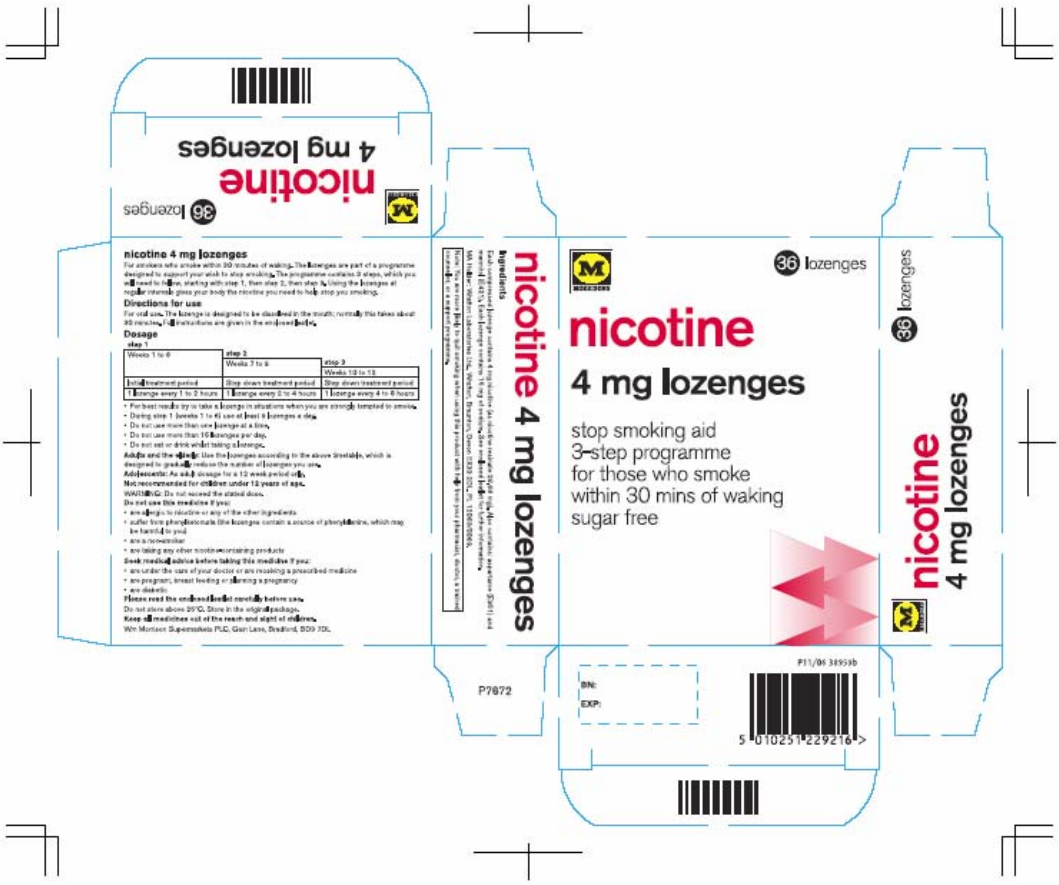
PACKAGING FOR THE 4MG LOZENGES




225.9mm
182mm
ASDA Nicotine
4 mg lozenges x 36
About This Product
Directions For Use
Dosage
ASDA Nicotine
4 mg lozenges
Ingredients
36 LOZENGES
36 LOZENGES
ASDA
SUGAR FREE
ASDA
Nicotine
4 mg lozenges
For those who smoke within 30 minutes of waking
Stop Smoking Aid
3 STEP PROGRAMME
Nicotine
4 mg lozenges
Stop Smoking Aid
P7753
BN
EXP
FAO MHRA:
Batch Number and Expiry date will be overprinted in this panel. Box to be print and varnish free.

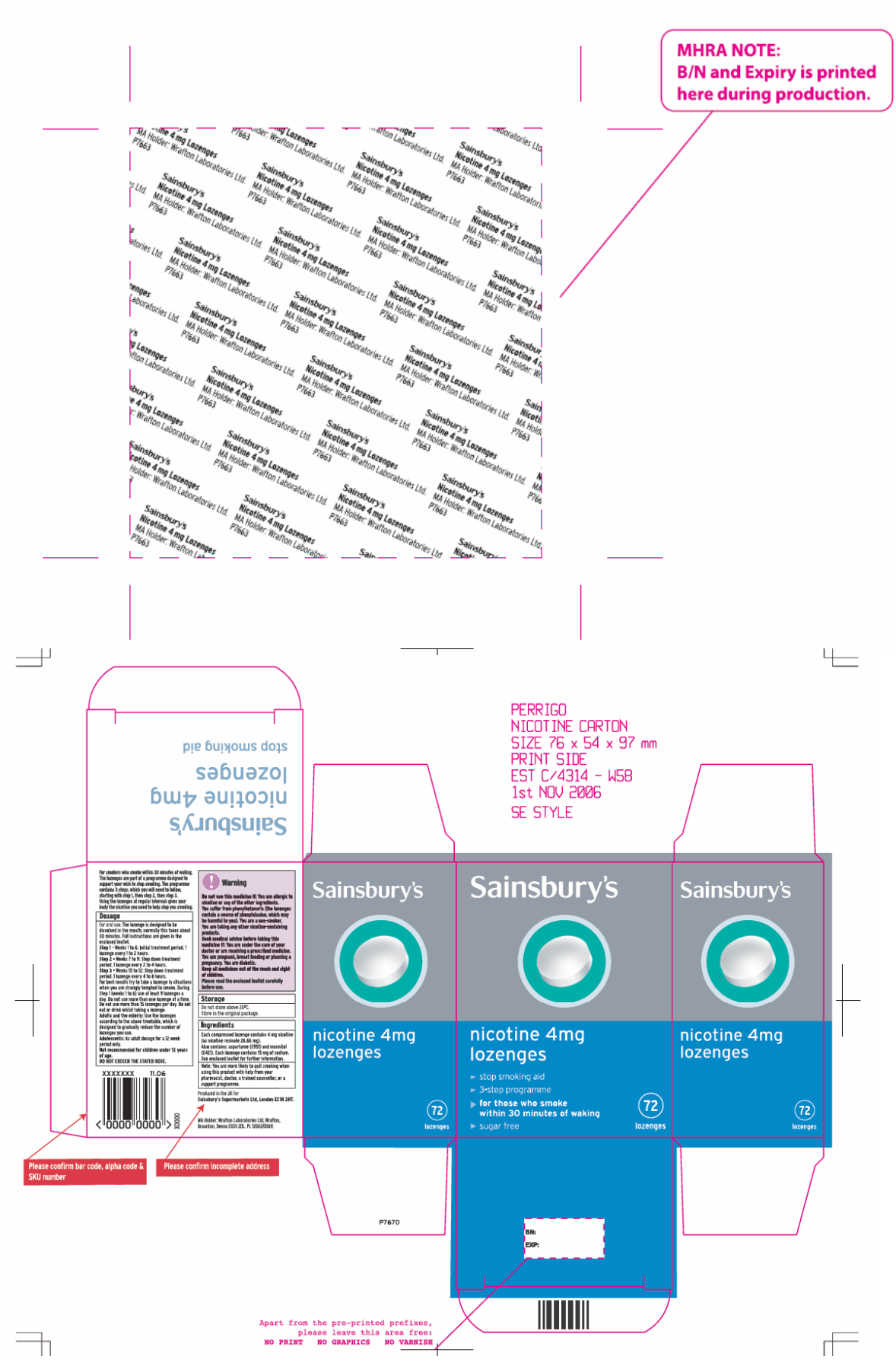
MHRA NOTE:
B/N and Expiry is printed here during production.

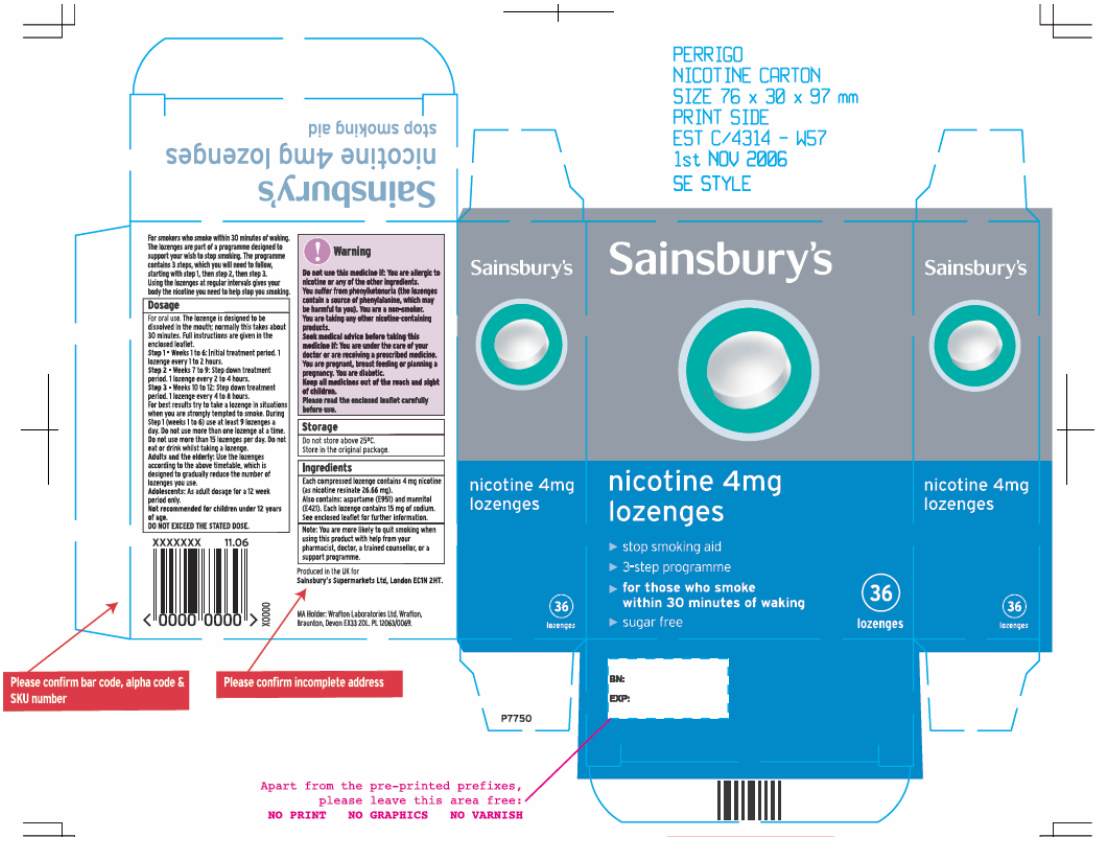




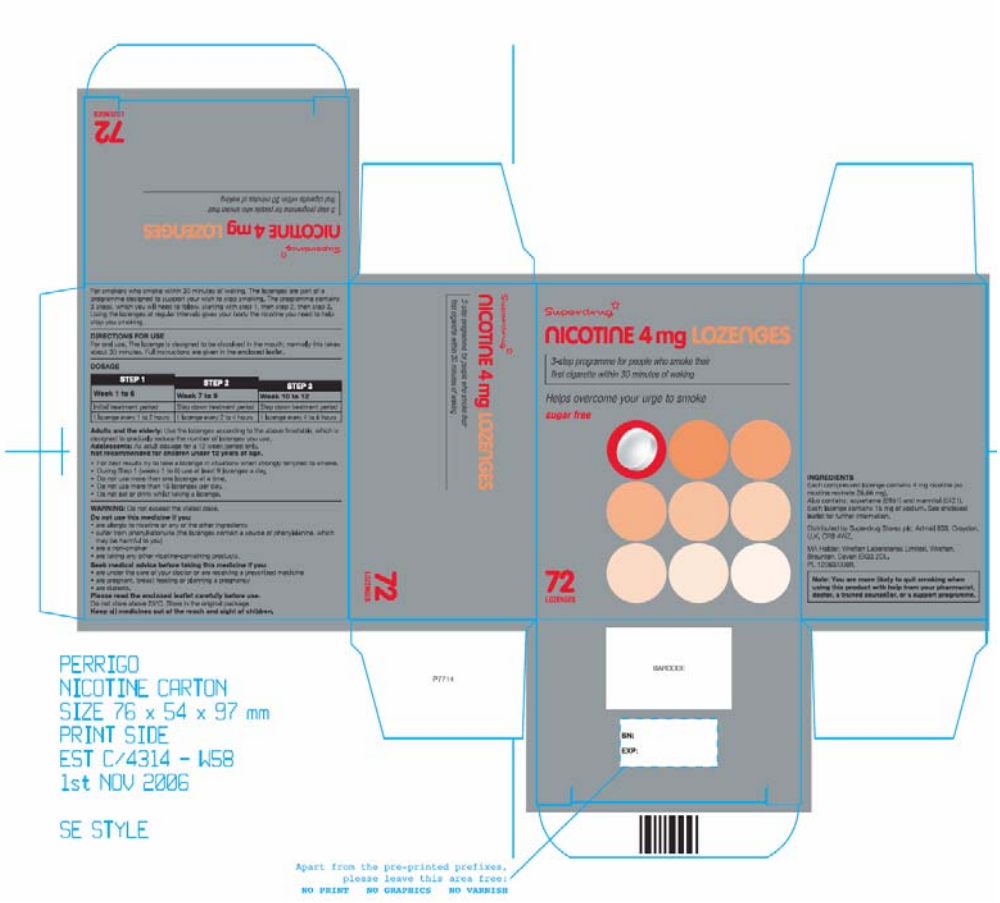
MHRA NOTE:
B/N and Expiry is printed here during production.


INE CARTON
76 x 30 x 97 mm
SIDE
/4314 - W57
JV 2006
YLE
paramed
NICOTINE
4mg LOZENGES
PARAMED® NICOTINE 4mg LOZENGES
Paramed Nicotine 4mg Lozenges are for smokers who smoke within 30 minutes of waking.
The lozenges are part of a programme designed to support your wish to stop smoking. The programme contains 3 steps, which you will need to follow, starting with step 1, then step 2, then step 3. Using the lozenges at regular intervals gives your body the nicotine you need to help stop you smoking.
DIRECTIONS FOR USE
For oral use. The lozenge is designed to be dissolved in the mouth, normally this takes about 30 minutes. Full instructions are given in the enclosed leaflet.
DOSAGE
STEP 1
Week 1 to 6
STEP 2
Week 7 to 9
STEP 3
Week 10 to 12
Initial treatment period.
Step down treatment period.
Step down treatment period.
1 lozenge every 1 to 2 hours
1 lozenge every 2 to 4 hours
1 lozenge every 4 to 8 hours
• For best results try to take a lozenge in situations when you are strongly tempted to smoke.
• During Step 1 (weeks 1 to 6) use at least 9 lozenges a day.
• Do not use more than one lozenge at a time.
• Do not use more than 15 lozenges per day.
• Do not eat or drink whilst taking a lozenge.
Adults and the elderly: Use the lozenges according to the above timetable, which is designed to gradually reduce the number of lozenges you use.
Adolescents: An adult dosage for a 12 week period only.
Not recommended for children under 12 years of age.
WARNING: Do not exceed the stated dose.
IMPORTANT
Please read the enclosed leaflet carefully before use
Keep all medicines out of the reach and sight of children
Do not use this medicine if you:
• are allergic to nicotine or any of the other ingredients
• suffer from phenylketonuria (the lozenges contain a source of phenylalanine, which may be harmful to you)
• are a non-smoker
• are taking any other nicotine-containing products.
Seek medical advice before taking this medicine if you:
• are under the care of your doctor or are receiving a prescribed medicine
• are pregnant, breast feeding or planning a pregnancy
• are diabetic.
INGREDIENTS
Each compressed lozenge contains 4 mg nicotine (as nicotine resinate 26.66 mg).
Also contains:
aspartame (E951) and mannitol (E421).
Each lozenge contains 15 mg of sodium.
See enclosed leaflet for further information.
Storage precautions:
Do not store above 25°C.
Store in the original package.
MA Holder:
Wrafton Laboratories Ltd., Wrafton, Braunton, Devon EX33 2DL. PL 12063/0069
'Paramed' is a registered trademark.
© Wrafton Laboratories Limited 2006.
paramed
NICOTINE
4mg LOZENGES
4mg
36 LOZENGES
paramed
NICOTINE
4mg LOZENGES
For those who smoke within 30 mins of waking
Sugar free
4mg
STOP SMOKING AID
36 LOZENGES
3-STEP PROGRAMME
You are more likely to quit smoking when using this product with help from your pharmacist, doctor, a trained counsellor, or a support programme.
P7674
BN:
EXP:
5 025331 101320
paramed
NICOTINE
4mg LOZENGES
4mg
36 LOZENGES
paramed
nicotine
#d mg
lozenges
Apart from the pre-printed prefixes, please leave this area free:
NO PRINT NO GRAPHICS NO VARNISH


MHRA NOTE:
B/N and Expiry is printed here during production.
Sainsbury's Nicotine 4 mg Lozenges
MA Holder: Wrafton Laboratories Ltd.
P7663
PERRIGO
NICOTINE CARTON
SIZE 76 x 54 x 97 mm
PRINT SIDE
EST C/4314 - W58
1st NOV 2006
SE STYLE
Sainsbury's
nicotine 4mg
lozenges
stop smoking aid
Warning
Dosage
Storage
Ingredients
Sainsbury's
nicotine 4mg lozenges
72 lozenges
stop smoking aid
3-step programme
for those who smoke within 30 minutes of waking
sugar free
BN:
EXP:
P7670
Please confirm bar code, alpha code & SKU number
Please confirm incomplete address
Apart from the pre-printed prefixes, please leave this area free:
NO PRINT NO GRAPHICS NO VARNISH


PERRIGO
NICOTINE CARTON
SIZE 76 x 30 x 97 mm
PRINT SIDE
EST C/4314 - W57
1st NOV 2006
SE STYLE
Sainsbury's nicotine 4mg lozenges stop smoking aid
Dosage
Warning
Storage
Ingredients
XXXXXX 11.06
Produced in the UK for Sainsbury's Supermarkets Ltd, London EC1N 2HT.
MA Holder: Wrafton Laboratories Ltd. Wrafton, Braunton, Devon EX33 2DL. PL 12063/0068.
Sainsbury's
nicotine 4mg lozenges
stop smoking aid
3-step programme
for those who smoke within 30 minutes of waking
sugar free
36 lozenges
BN:
EXP:
P7750
Please confirm bar code, alpha code & SKU number
Please confirm incomplete address
Apart from the pre-printed prefixes, please leave this area free:
NO PRINT NO GRAPHICS NO VARNISH

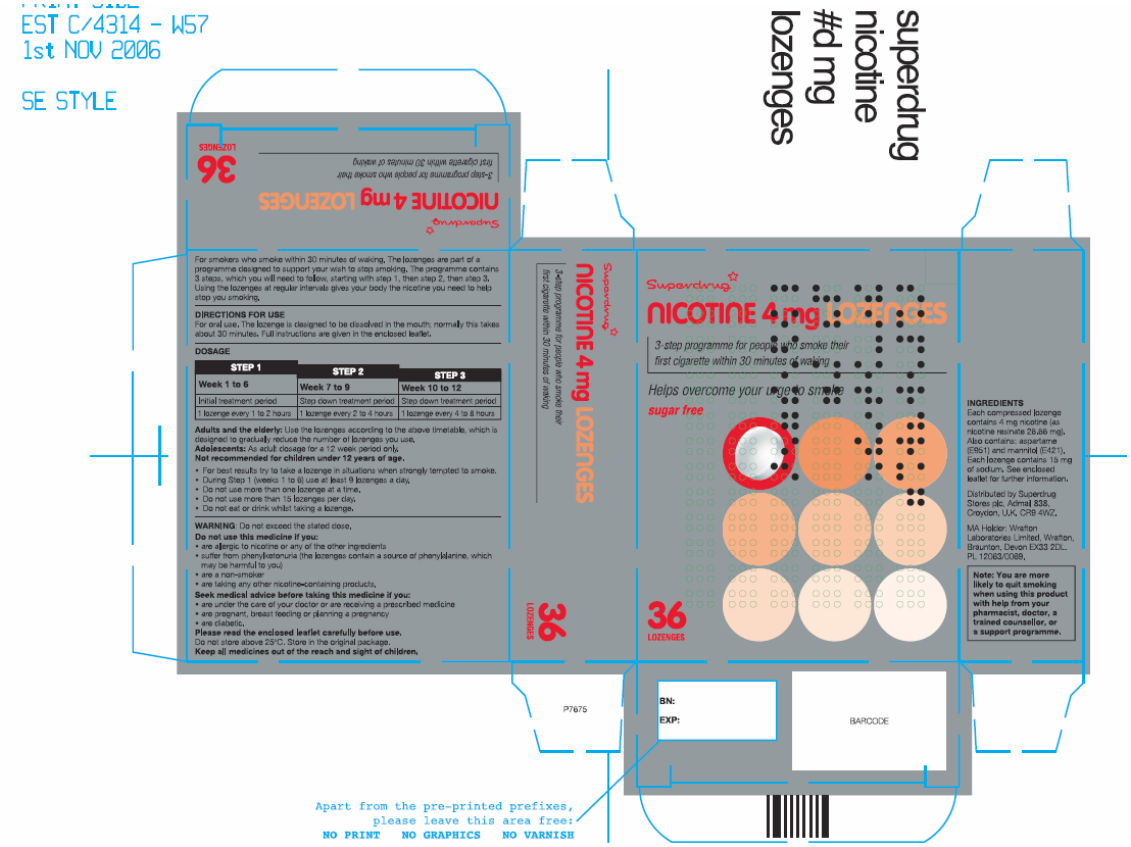
MHRA NOTE:
B/N and Expiry is printed here during production.

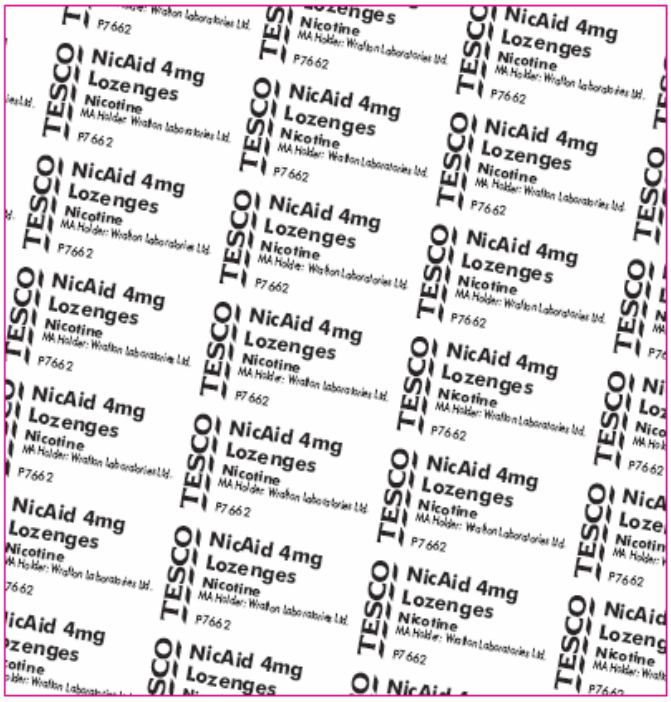


PERRIGO
NICOTINE CARTON
SIZE 76 x 54 x 97 mm
PRINT SIDE
EST C/4314 - W58
1st NOV 2006

SE STYLE

Apart from the pre-printed prefixes, please leave this area free:
NO PRINT NO GRAPHICS NO VARNISH


EST C/4314 - W57
1st NOV 2006
SE STYLE
superdrug
nicotine
#d mg
lozenges
NICOTINE 4 mg LOZENGES
36
LOZENGES
For smokers who smoke within 30 minutes of waking. The lozenges are part of a programme designed to support your wish to stop smoking. The programme contains 3 steps, which you will need to follow, starting with step 1, then step 2, then step 3. Using the lozenges at regular intervals gives your body the nicotine you need to help stop you smoking.
DIRECTIONS FOR USE
For oral use. The lozenge is designed to be dissolved in the mouth; normally this takes about 30 minutes. Full instructions are given in the enclosed leaflet.
DOSAGE
STEP 1
STEP 2
STEP 3
Week 1 to 6
Week 7 to 9
Week 10 to 12
Initial treatment period
Step down treatment period
Step down treatment period
1 lozenge every 1 to 2 hours
1 lozenge every 2 to 4 hours
1 lozenge every 4 to 8 hours
Adults and the elderly: Use the lozenges according to the above timetable, which is designed to gradually reduce the number of lozenges you use.
Adolescents: As adult dosage (for a 12 week period only).
Not recommended for children under 12 years of age.
• For best results try to take a lozenge in situations when strongly tempted to smoke.
• During Step 1 (weeks 1 to 6) use at least 9 lozenges a day.
• Do not use more than one lozenge at a time.
• Do not use more than 15 lozenges per day.
• Do not eat or drink whilst taking a lozenge.
WARNING. Do not exceed the stated dose.
Do not use this medicine if you:
• are allergic to nicotine or any of the other ingredients
• suffer from phenylketonuria (the lozenges contain a source of phenylalanine, which may be harmful to you)
• are a non-smoker
• are taking any other nicotine-containing products.
Seek medical advice before taking this medicine if you:
• are under the care of your doctor or are receiving a prescribed medicine
• are pregnant, breast feeding or planning a pregnancy
• are diabetic.
Please read the enclosed leaflet carefully before use.
Do not store above 25°C. Store in the original package.
Keep all medicines out of the reach and sight of children.
Superdrug
NICOTINE 4 mg LOZENGES
3-step programme for people who smoke their first cigarette within 30 minutes of waking
Helps overcome your urge to smoke
sugar free
36
LOZENGES
INGREDIENTS
Each compressed lozenge contains 4 mg nicotine (as nicotine resinate 26.66 mg). Also contains: aspartame (E951) and mannitol (E421). Each lozenge contains 15 mg of sodium. See enclosed leaflet for further information.
Distributed by Superdrug Stores plc, Admail 838, Croydon, UK, CR9 4WZ.
MA Holder: Wrafton Laboratories Limited, Wrafton, Braunton, Devon EX33 2DL. PL 12063/0068.
Note: You are more likely to quit smoking when using this product with help from your pharmacist, doctor, a trained counsellor, or a support programme.
P7675
BN:
EXP:
BARCODE
Apart from the pre-printed prefixes, please leave this area free:
NO PRINT NO GRAPHICS NO VARNISH


TESCO
NicAid 4mg
Lozenges
Nicotine
MA Holder: Wrafton Laboratories Ltd.
P7662


for version 2, requests for the heading 'Tesco NicAid 4 mg Lozenges' to be in brail on the front face.
TESCO
NicAid
4 mg Lozenges
Nicotine
72 lozenges
4 mg
• For those who smoke within 30 mins of waking
• Sugar free
Tesco NicAid 4 mg Lozenges
WARNINGS
Dosage
Ingredients
Storage
Do not use
P7069
BN:
EXP:

MHRA NOTE:
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