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NIQUITIN MINIS 1.5MG LOZENGES
PL 00079/0658
NIQUITIN MINIS 4MG LOZENGES
PL 00079/0659

LAY SUMMARY

The MHRA granted Beecham Group plc Marketing Authorisations (licences) for the medicinal products NiQuitin Minis 1.5mg Lozenges and NiQuitin Minis 4mg Lozenges on 10th March 2010. These products are available on the General sale list (GSL). NiQuitin Lozenges are a stop smoking aid. They can help you give up smoking straightaway, to cut down smoking before stopping completely or to stop smoking for short periods of time.

NiQuitin Lozenges 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 unpleasant symptoms, such as feeling ill or irritable, that smokers often feel when they try to give up or when they are in situations where they cannot have a cigarette. The nicotine can also reduce your cravings for a cigarette and help you to resist the urge to smoke.

These applications are duplicates of previously granted applications for NiQuitin Minis Mint 1.5mg Lozenges and NiQuitin Minis Mint 4mg Lozenges (PL 00079/0610-611), for which the marketing authorisation holder is Beecham Group plc and which were granted licences on 12th February 2009.

No new or unexpected safety concerns arose from these simple applications and it was, therefore, judged that the benefits of taking NiQuitin Minis 1.5mg Lozenges and NiQuitin Minis 4mg Lozenges outweigh the risks, hence Marketing Authorisations have been granted.
NIQUITIN MINIS 1.5MG LOZENGES
PL 00079/0658
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SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted marketing authorisations for the medicinal products NiQuitin Minis 1.5mg Lozenges and NiQuitin Minis 4mg Lozenges (PL 00079/0658-9) to Beecham Group plc on 10th March 2010. The products are available as general-sales licence medicines (GSL) for the treatment of tobacco dependence by relief of nicotine withdrawal symptoms, including cravings. Permanent cessation of tobacco use is the eventual objective. NiQuitin Minis 1.5 and 4mg Lozenges can be used:

- for smoking cessation (abrupt and gradual)
- as an aid for smokers during temporary abstinence

NiQuitin Minis 1.5 and 4mg Lozenges should preferably be used in conjunction with a behavioural support programme.

NiQuitin Lozenges work by replacing some of the nicotine you are used to getting from cigarettes. It is the nicotine in cigarettes that can make you physically addicted to them. This type of treatment is called Nicotine Replacement Therapy (NRT).

The applications were submitted as a simple abridged applications according to Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC, cross-referring to NiQuitin Minis Mint 1.5mg Lozenges and NiQuitin Minis Mint 4mg Lozenges (PL 00079/0610-611), for which the marketing authorisation holder is Beecham Group plc and which were granted licences on 12th February 2009.

No new data were submitted nor were they necessary for these simple applications, as the data are identical to that of the previously granted cross-reference products.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 00079/0658-9
PROPRIETARY NAME: NiQuitin Minis 1.5 and 4mg Lozenges
ACTIVE(S): Nicotine (as Nicotine Resinate Ph. Eur.)
COMPANY NAME: Beecham Group plc
LEGAL STATUS: GSL

1. INTRODUCTION
These are a simple, piggy back applications for NiQuitin Minis 1.5 and 4mg Lozenges submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is Beecham Group plc, 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom (T/A GlaxoSmithKline Consumer Healthcare, Brentford TW8 9GS, UK).

The applications cross-refer to NiQuitin Minis Mint 1.5mg Lozenges and NiQuitin Minis Mint 4mg Lozenges (PL 00079/0610-611), for which the marketing authorisation holder is Beecham Group plc and which were granted licences on 12th February 2009. The current applications are considered valid.

2. MARKETING AUTHORIZATION APPLICATION FORM

2.1 Name(s)
The proposed names of the products are NiQuitin Minis 1.5mg Lozenges and NiQuitin Minis 4mg Lozenges. The products have been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
The products contain nicotine, equivalent to 1.5 or 4mg. They are to be stored in child-resistant polypropylene tablet container/cap, incorporating a molecular sieve desiccant (sodium alumino silicate) and containing 20 lozenges. Packs may contain 1 or 3 tablet containers.

The proposed shelf-life (3 years) and storage conditions (Do not store above 30°C. Store in the original package in order to protect the product from moisture) are consistent with the details registered for the cross-reference products.

2.3 Legal status
On approval, the products will be available as general sales licence medicines (GSL).

2.4 Marketing authorisation holder/Contact Persons/Company
Beecham Group plc, 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom (T/A GlaxoSmithKline Consumer Healthcare, Brentford TW8 9GS, UK).

The QP responsible for pharmacovigilance is stated and his CV is included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference products and evidence of GMP compliance has been provided.
2.6 Qualitative and quantitative composition
The proposed compositions are consistent with the details registered for the cross-reference products.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch sizes are stated.

2.8 Finished product/shelf-life specification
The proposed finished product specifications are in line with the details registered for the cross-reference products.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference products.

2.10 TSE Compliance
No materials of animal or human origin are included in the product. This is consistent with the cross reference products.

3. EXPERT REPORTS
The applicant has included detailed expert reports in Module 2 of the applications. Signed declarations and copies of the experts’ CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The appearances of the products are identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed summaries are consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET/CARTON
PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference products.

Carton and blister
The proposed artwork is comparable to the artwork registered for the cross-reference products and complies with statutory requirements. In-line with current legislation, the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.
7. CONCLUSIONS
The data submitted with the applications are acceptable. Marketing Authorisations should be granted.
PRECLINICAL ASSESSMENT

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

No new clinical data have been supplied with these applications and none are required for applications of this type.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for these applications are consistent with that previously assessed for the cross-reference products and as such have been judged to be satisfactory.

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

EFFICACY
These applications are identical to previously granted applications for NiQuitin Minis Mint 1.5mg Lozenges and NiQuitin Minis Mint 4mg Lozenges (PL 00079/0610-611).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference products.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products. 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.
### STEPS TAKEN FOR ASSESMENT

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 16/07/2009.</td>
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<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 30/07/2009.</td>
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<td>The MHRA sent requests for further information (RFI’s) on 24/10/2009 and 08/01/2010.</td>
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<td>Responses to the RFI’s were received on 09/12/2009 and 05/02/2010</td>
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<td>The applications were determined on 08/03/2010</td>
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### STEPS TAKEN AFTER ASSESSMENT

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NIQUITIN MINIS 1.5MG LOZENGES
PL 00079/0658
NIQUITIN MINIS 4MG LOZENGES
PL 00079/0659

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
NiQuitin Minis 1.5 mg Lozenges

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each lozenge contains 1.5 mg nicotine (as nicotine resinate).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Compressed Lozenge (lozenge)
White to off white oval tablet with convex surfaces; one surface bearing a debossed “L” logo.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
NiQuitin Minis 1.5 mg Lozenges are for the treatment of tobacco dependence by relief of nicotine withdrawal symptoms including cravings. Permanent cessation of tobacco use is the eventual objective. NiQuitin Minis 1.5 mg Lozenges can be used:
• for smoking cessation (abrupt and gradual)
• as an aid for smokers during temporary abstinence
NiQuitin Minis 1.5 mg Lozenges should preferably be used in conjunction with a behavioural support programme.

4.2 Posology and method of administration
Directions for use:
The strength of lozenge to be used will depend on the smoking habits of the individual.
NiQuitin Minis 1.5 mg Lozenges are suitable for smokers who smoke 20 cigarettes or less a day.

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 10 minutes). The lozenge should not be chewed or swallowed whole.

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

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

Adults (18 year and over)
Abrupt cessation of smoking:
Users should make every effort to stop smoking completely during treatment with NiQuitin Minis 1.5 mg Lozenges.

Use the lozenges whenever there is an urge to smoke.
Sufficient lozenges should be used each day, usually 8-12, up to a maximum of 15.

Continue use for up to six weeks to break the habit of smoking, then gradually reduce lozenge use. When daily use is 1-2 lozenges, use should be stopped.

To help stay smoke free after treatment, users may take a lozenge in situations when they are strongly tempted to smoke.
Those who use lozenges beyond 9 months are recommended to seek additional help and advice from a healthcare professional.

**Gradual cessation of smoking:**
For smokers who are unwilling or unable to quit abruptly.

Use a lozenge whenever there is a strong urge to smoke in order to reduce the number of cigarettes smoked as far as possible and to refrain from smoking as long as possible.

The number of lozenges a day is variable and depends on the patients' needs. Nonetheless it should not exceed 15 lozenges per day.

If a reduction in cigarette consumption has not been achieved after 6 weeks of treatment, a healthcare professional should be consulted.

Reduced tobacco consumption should lead to complete cessation of smoking. This should be attempted as soon as possible. When the number of cigarettes has been reduced to a level from which the user feels able to quit completely, then start on the schedule for “abrupt cessation” as given above.

If the attempt to stop smoking completely has not been started within 6 months after the beginning of treatment, it is recommended to consult a healthcare professional.

**Temporary Abstinence**
Use a lozenge every 1-2 hours to control troublesome withdrawal symptoms including craving. Users should not take more than 15 lozenges per day. Users should be encouraged to stop smoking completely as soon as possible. If users are still feeling the need to use the lozenges on a regular basis 6 months after the start of treatment and have still been unable to undertake a permanent quit attempt, then it is recommended to seek additional help and advice from a healthcare professional.

**Children and adolescents:**
Adolescents (12-17 years) should follow the schedule of treatment for abrupt cessation of smoking as given above, but restrict use to a maximum of 12 weeks duration. If longer treatment is required, or where adolescents are not ready or able to stop smoking abruptly, advice from a healthcare professional should be sought.

Safety and effectiveness in children who smoke have not been evaluated. NiQuitin Minis 1.5 mg Lozenges are not recommended for use in children under the age of 12.

### 4.3 Contraindications
NiQuitin Minis 1.5 mg Lozenges are contraindicated in:
- those with 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 hospitalised 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, NiQuitin Minis 1.5 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 effects.

- **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 preparations should be used with caution in these conditions. Ulcerative stomatitis has been reported.

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

**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.

### 4.5 Interaction with other medicinal products and other forms of interaction

No clinically relevant interactions between nicotine replacement therapy and other drugs have definitely been established, however nicotine may possibly enhance the haemodynamic effects of adenosine.

### 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 fetus 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 fetus affecting breathing movements and has a dose dependent effect on placental/fetal 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**

Nicotine from smoking and NRT is found in breast milk. However the amount of nicotine the infant is exposed to from NRT 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 relevant.
4.8 Undesirable effects
NRT can cause adverse reactions similar to those associated with nicotine administered in other ways, including smoking. These may be attributed to the pharmacological effects of nicotine, some of which are dose dependent. At recommended doses NiQuitin Minis 1.5 mg Lozenges have not been found to cause any serious adverse effects. Excessive consumption of NiQuitin Minis by those who have not been in the habit of inhaling tobacco smoke could possible lead to nausea, faintness or headaches.

Certain symptoms which have been reported such as depression, irritability, anxiety, increased appetite 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.

Immune system disorders
Very rare (<1/10000): anaphylactic reactions

Psychiatric disorders
Common (>1/100, <1/10): irritability, anxiety, sleep disorders incl. abnormal dreams
Uncommon (>1/1000, <1/100): nervousness, depression

Nervous system disorders:
Common (>1/100, <1/10): dizziness, headaches

Cardiac Disorders
Uncommon (>1/1000, <1/100): palpitations, heart rate increased

Respiratory, thoracic and mediastinal disorders
Common (>1/100, <1/10): cough, sore throat

Gastrointestinal disorders
Very common (>1/10): nausea, mouth/throat and tongue irritation
Common (>1/100, <1/10): vomiting, diarrhoea, gastro-intestinal discomfort, flatulence, hiccups, heartburn, dyspepsia

Skin and Subcutaneous Tissue Disorders
Uncommon (>1/1000, <1/100): rash

General Disorders and Administration Site Conditions
Uncommon (>1/1000, <1/100): fatigue, malaise, chest pain

4.9 Overdose
Symptoms: The minimum lethal dose of nicotine in a non-tolerant man has been estimated to be 40 to 60 mg. Symptoms of acute nicotine poisoning include nausea, 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 cease immediately and the patient should be treated symptomatically. Artificial respiration with oxygen should be instituted if necessary. Activated charcoal reduces the gastro-intestinal absorption of nicotine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in nicotine dependence.
ATC Code: N07B A01

Nicotine is an agonist at nicotine receptors in the peripheral and central nervous system and has pronounced CNS and cardiovascular effects. 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. Cravings and other symptoms of nicotine withdrawal are at their most intense during the first few weeks of a quit attempt, diminishing thereafter. The lozenges replace some of the nicotine provided by tobacco and clinical studies measuring intensity of cravings and other withdrawal symptoms have been shown to alleviate these symptoms when they are at their most intense.

5.2 Pharmacokinetic properties

NiQuitin Minis Lozenges dissolve completely 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 NiQuitin Minis Lozenges is typically achieved in 10 minutes. When dosed every hour, the steady state mean $C_{\text{max}}$ and $C_{\text{min}}$ concentrations are 18.4 and 15.0 ng/ml respectively.

As the plasma protein binding of nicotine is low (4.9%), 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.

NiQuitin 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 NiQuitin Minis 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 NiQuitin Minis Lozenges indicate that the potential risk is low and outweighed by the demonstrable benefit of nicotine therapy in smoking cessation. However, NiQuitin Minis 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 (E421)
Sodium alginate (E401)
Xanthan gum (E415)
Potassium bicarbonate (E501)
Calcium polycarbophil
Sodium carbonate anhydrous (E500)
Acesulfame potassium (E950)
Taste Masking Flavour 031431
Peppermint Flavour 022173
Menthol Flavour 020184
Magnesium Stearate (E470b)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Do not store above 30°C. Store in the original package in order to protect the product from moisture.

6.5 Nature and contents of container
Child resistant polypropylene tablet container/cap incorporating a molecular sieve desiccant (sodium aluminosilicate) and containing 20 lozenges

Packs may contain 1 or 3 tablet containers.

Not all pack sizes may be marketed.

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

7 MARKETING AUTHORISATION HOLDER
Beecham Group plc
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom
T/A GlaxoSmithKline Consumer Healthcare
Brentford TW8 9GS, UK.

8 MARKETING AUTHORISATION NUMBER(S)
PL 00079/0658

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/03/2010

10 DATE OF REVISION OF THE TEXT
10/03/2010
NAME OF THE MEDICINAL PRODUCT
NiQuitin Minis 4 mg Lozenges

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each lozenge contains 4 mg nicotine (as nicotine resinate).
For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM
Compressed Lozenge (lozenge)

White to off white oval tablet with convex surfaces; one surface bearing a debossed “F” logo.

CLINICAL PARTICULARS

Therapeutic indications
NiQuitin Minis 4 mg Lozenges are for the treatment of tobacco dependence by relief of nicotine withdrawal symptoms including cravings. Permanent cessation of tobacco use is the eventual objective. NiQuitin Minis 4 mg Lozenges can be used:
- for smoking cessation (abrupt and gradual)
- as an aid for smokers during temporary abstinence

NiQuitin Minis 4 mg Lozenges should preferably be used in conjunction with a behavioural support programme.

Posology and method of administration

Directions for use:
The strength of lozenge to be used will depend on the smoking habits of the individual.

NiQuitin Minis 4 mg Lozenges are suitable for smokers who smoke more than 20 cigarettes a day.

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 10 minutes). The lozenge should not be chewed or swallowed whole.

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

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

Adults (18 year and over)

Abrupt cessation of smoking:
Users should make every effort to stop smoking completely during treatment with NiQuitin Minis 4 mg Lozenges.

Use the lozenges whenever there is an urge to smoke.
Sufficient lozenges should be used each day, usually 8-12, up to a maximum of 15.

Continue use for up to six weeks to break the habit of smoking, then gradually reduce lozenge use. When daily use is 1-2 lozenges, use should be stopped.

To help stay smoke free after treatment, users may take a lozenge in situations when they are strongly tempted to smoke.

Those who use lozenges beyond 9 months are recommended to seek additional help and advice from a healthcare professional.
**Gradual cessation of smoking:**
For smokers who are unwilling or unable to quit abruptly.

Use a lozenge whenever there is a strong urge to smoke in order to reduce the number of cigarettes smoked as far as possible and to refrain from smoking as long as possible.

The number of lozenges a day is variable and depends on the patients needs. Nonetheless it should not exceed 15 lozenges per day.

If a reduction in cigarette consumption has not been achieved after 6 weeks of treatment, a healthcare professional should be consulted.

Reduced tobacco consumption should lead to complete cessation of smoking. This should be attempted as soon as possible. When the number of cigarettes has been reduced to a level from which the user feels able to quit completely, then start on the schedule for “abrupt cessation” as given above.

If the attempt to stop smoking completely has not been started within 6 months after the beginning of treatment, it is recommended to consult a healthcare professional.

**Temporary Abstinence**
Use a lozenge every 1-2 hours to control troublesome withdrawal symptoms including craving. Users should not take more than 15 lozenges per day. Users should be encouraged to stop smoking completely as soon as possible. If users are still feeling the need to use the lozenges on a regular basis 6 months after the start of treatment and have still been unable to undertake a permanent quit attempt, then it is recommended to seek additional help and advice from a healthcare professional.

**Children and adolescents:**
Adolescents (12-17 years) should follow the schedule of treatment for abrupt cessation of smoking as given above, but restrict use to a maximum of 12 weeks duration. If longer treatment is required, or where adolescents are not ready or able to stop smoking abruptly, advice from a healthcare professional should be sought.

Safety and effectiveness in children who smoke have not been evaluated. NiQuitin Minis 4 mg Lozenges are not recommended for use in children under the age of 12.

### 4.3 Contraindications
NiQuitin Minis 4 mg Lozenges are contraindicated in:
- those with 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 hospitalised 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, NiQuitin Minis 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 effects.

- **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 preparations should be used with caution in these conditions. Ulcerative stomatitis has been reported.

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

**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.

4.5 **Interaction with other medicinal products and other forms of interaction**

No clinically relevant interactions between nicotine replacement therapy and other drugs have definitely been established, however nicotine may possibly enhance the haemodynamic effects of adenosine.

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 fetus 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 fetus affecting breathing movements and has a dose dependent effect on placental/fetal 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**

Nicotine from smoking and NRT is found in breast milk. However the amount of nicotine the infant is exposed to from NRT 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 relevant.
4.8 Undesirable effects
NRT can cause adverse reactions similar to those associated with nicotine administered in other ways, including smoking. These may be attributed to the pharmacological effects of nicotine, some of which are dose dependent. At recommended doses NiQuitin Minis 4 mg Lozenges have not been found to cause any serious adverse effects. Excessive consumption of NiQuitin Minis by those who have not been in the habit of inhaling tobacco smoke could possible lead to nausea, faintness or headaches.

Certain symptoms which have been reported such as depression, irritability, anxiety, increased appetite 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.

Immune system disorders
Very rare (<1/10000): anaphylactic reactions

Psychiatric disorders
Common (>1/100, <1/10): irritability, anxiety, sleep disorders incl. abnormal dreams

Uncommon (>1/1000, <1/100): nervousness, depression

Nervous system disorders:
Common (>1/100, <1/10): dizziness, headaches

Cardiac Disorders
Uncommon (>1/1000, <1/100): palpitations, heart rate increased

Respiratory, thoracic and mediastinal disorders
Common (>1/100, <1/10): cough, sore throat

Gastrointestinal disorders
Very common (>1/10): nausea, mouth/throat and tongue irritation

Common (>1/100, <1/10): vomiting, diarrhoea, gastro-intestinal discomfort, flatulence, hiccups, heartburn, dyspepsia

Skin and Subcutaneous Tissue Disorders
Uncommon (>1/1000, <1/100): rash

General Disorders and Administration Site Conditions
Uncommon (>1/1000, <1/100): fatigue, malaise, chest pain

4.9 Overdose
Symptoms: The minimum lethal dose of nicotine in a non-tolerant man has been estimated to be 40 to 60 mg. Symptoms of acute nicotine poisoning include nausea, 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 cease immediately and the patient should be treated symptomatically. Artificial respiration with oxygen should be instituted if necessary. Activated charcoal reduces the gastro-intestinal absorption of nicotine.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Drugs used in nicotine dependence.
ATC Code: N07B A01

Nicotine is an agonist at nicotine receptors in the peripheral and central nervous system and has pronounced CNS and cardiovascular effects. 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. Cravings and other symptoms of nicotine withdrawal are at their most intense during the first few weeks of a quit attempt, diminishing thereafter. The lozenges replace some of the nicotine provided by tobacco and clinical studies measuring intensity of cravings and other withdrawal symptoms have been shown to alleviate these symptoms when they are at their most intense.

5.2 Pharmacokinetic properties
NiQuitin Minis Lozenges dissolve completely 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 NiQuitin Minis Lozenges is typically achieved in 10 minutes. The mean peak plasma concentrations of nicotine achieved after single 4 mg dose are approximately 9.1 ng/ml.

As the plasma protein binding of nicotine is low (4.9%), 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 NiQuitin Minis 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 NiQuitin Minis Lozenges indicate that the potential risk is low and outweighed by the demonstrable benefit of nicotine therapy in smoking cessation. However, NiQuitin Minis 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 (E421)
Sodium alginate (E401)
Xanthan gum (E415)
Potassium bicarbonate (E501)
Calcium polycarbophil
Sodium carbonate anhydrous (E500)
Acesulfame potassium (E950)
Taste Masking Flavour 031431
Peppermint Flavour 022173
Menthol Flavour 020184
Magnesium Stearate (E470b)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Do not store above 30°C. Store in the original package in order to protect the product from moisture.

6.5 Nature and contents of container
Child resistant polypropylene tablet container/cap incorporating a molecular sieve desiccant (sodium aluminosilicate) and containing 20 lozenges

Packs may contain 1 or 3 tablet containers.

Not all pack sizes may be marketed.

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

7 MARKETING AUTHORISATION HOLDER
Beecham Group plc
980 Great West Road
Brentford
Middlesex
TW8 9GS
United Kingdom
T/A GlaxoSmithKline Consumer Healthcare
Brentford TW8 9GS, UK.

8 MARKETING AUTHORISATION NUMBER(S)
PL 00079/0659

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/03/2010

10 DATE OF REVISION OF THE TEXT
10/03/2010
PATIENT INFORMATION LEAFLET

1. What NiQuitin Minis do

These tablets of treated nicotine Replacement Therapy or NRT. NiQuitin Minis come in two strengths, 1.5 mg or 4 mg each tablet.

NiQuitin Minis 1.5 mg lozenges are for smokers who smoke two or more cigarettes a day.

NiQuitin Minis 4 mg lozenges are for smokers who smoke three or more cigarettes a day.

NiQuitin Minis help to prevent nicotine withdrawal symptoms that may occur when you stop smoking.

1.2. How NiQuitin Minis work

NiQuitin Minis work by releasing nicotine into the body. This is because they contain less tar, less carbon monoxide and less other tobacco-related chemicals.

When you put NiQuitin Minis in your mouth, the nicotine is released into the blood.

The nicotine is absorbed into the body, and helps to reduce the urge to smoke.

1.3. Side effects

Some people may experience side effects, such as headache, stomach upset, or changes in bowel habits.

1.4. About the medicine

NiQuitin Minis are not suitable for use in pregnancy or while breastfeeding. If you are pregnant or breastfeeding, please consult your doctor or pharmacist before using NiQuitin Minis.

2. Check before you take NiQuitin Minis

2.1. Do not use NiQuitin Minis if

You are allergic to any of the ingredients in the lozenges (see Section 6.2 for more information).

You are under the age of 15.

2.2. Before you take NiQuitin Minis

It is important to talk to your doctor or pharmacist before taking NiQuitin Minis to make sure they are safe for you to use.

3. How to use NiQuitin Minis

3.1. Using the tablets

NiQuitin Minis are to be used in the mouth. The tablet should be held between your teeth and beneath your gum, but not under your tongue.

3.2. Stopping smoking

If you stop smoking, you should stop using NiQuitin Minis. It is advisable to stop using NiQuitin Minis gradually.

3.3. Discontinuing treatment

If you have been using NiQuitin Minis for a long time, you should gradually reduce your dose before stopping completely.

3.4. Taking other medicines

NiQuitin Minis can be taken with other medicines, but you should always check with your doctor or pharmacist before taking any other medicines.

4. What you should know about NiQuitin Minis

NiQuitin Minis are not a substitute for advice from a healthcare professional.

5. How to report side effects

If you experience any side effects that you think may be due to NiQuitin Minis, please consult your doctor or pharmacist.

6. Additional information

For more information, please refer to the manufacturer's leaflet.
LABELLING

NiQuitin Minis
1.5 mg lozenges Nicotine

HELPS OVERCOME YOUR URGE TO SMOKE
LOW STRENGTH
For those who smoke 20 cigarettes or less a day

20 LOZENGE PACK

NiQuitin Minis
1.5 mg lozenges Nicotine

STOPPING SMOKING STRAIGHTAWAY is best for your health. However, if you are not able to, you can also use NiQuitin Minis to help you cut down before stopping or to help you stop smoking for short periods of time. For full instructions please read the enclosed leaflet carefully.

DO NOT USE
• If you are allergic to any of the ingredients listed below.
• If you are a non-smoker or under the age of 12 years.
• If you are in hospital because of heart problems unless your doctor tells you to.

CONSULT A HEALTHCARE PROFESSIONAL
• If you have serious liver or kidney illness, uncontrolled diabetes, or taking any other medication.
• If you have a cold, or a throat infection.
• If you are pregnant or breastfeeding.

INGREDIENTS
Each lozenge contains 1.5 mg nicotine (nicotine retina). Also contains: mannitol (E421), sucrose, gum arabic (E414), tremella fuciformis (E410), calcium carbonate, sucrose, saccharin sodium, sodium saccharin, yellow lake, red lake, blue lake, carmine, oil of peppermint, preservatives (E223).

Keep away from children. Do not use above 30°C. Keep lozenges in the original package.
NiQuitin Minis 1.5 and 4 mg Lozenges (PL 00079/0658-9)

Please read the leaflet carefully before using this product. Dissolve 1 lozenge in the mouth over 10 minutes. Maximum 15 lozenges per day. Keep out of reach and sight of children. Do not store above 30°C. Store in original container. Contains 20 lozenges.

GlaxoSmithKline Consumer Healthcare

PL 00079/0658
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NiQuitin Minis 4 mg lozenges nicotine

HELPERS OVERCOME YOUR URGE TO SMOKE
FULL STRENGTH
For those who smoke more than 20 cigarettes a day

20 LOZENGE PACK

HOW TO USE
Put one NiQuitin Minis in your mouth and allow to dissolve fully. This should take around 5 minutes.

Adults and children 12 years and over: When stopping smoking straightaway, have a NiQuitin Minis when you have an urge to smoke. Use 8 to 12 a day (maximum 13) for up to 4 weeks, then gradually phase out their use. Stop using NiQuitin Minis when you are using 1 or 2 a day.

Adults 15 years and over: If you are cutting down before stopping completely, have a NiQuitin Minis instead of a cigarette when you feel a strong urge to smoke. Cut down your cigarettes by as many as possible. Quit as soon as you feel able, then follow the instructions for stopping smoking straightaway.

If you are stopping smoking for short periods of time, have a NiQuitin Minis instead of a cigarette when you feel a strong urge to smoke. Use a NiQuitin Minis every 1-2 hours.

DO NOT USE
- If you are allergic to any of the ingredients listed below.
- If you are a non-smoker or under the age of 12 years.
- If you have inhaled because of heart problems unless your doctor tells you to.

CONSULT A HEALTHCARE PROFESSIONAL
- If you have serious liver or kidney disease, uncontrolled hypertension, thyroid gland or pheochromocytoma, stomach ulcer or other problems with your stomach or throat.
- Before use if you are pregnant or breastfeeding.

QUALITIES
Each lozenge contains 4 mg nicotine (as nicotine retina). Also contains mannitol (E 421), sodium alginate (E 404), xanthan gum (E 415), potassium bicarbonate (E 241), calcium pyrophosphate, sodium carbonate anhydrous (E 965), acacia/cellosolve potassium (E812), magnesium stearate (E 470) and flavour.

Keep out of the reach and sight of children.
Do not store above 30°C.

Keep lozenges in the original package.