Public Assessment Report

UKPAR

Nicotine Mint 2 mg and 4 mg Medicated Chewing Gum
Nicotine Fruit 2 mg and 4 mg medicated Chewing Gum

(Nicotine resinate)

UK Licence No: PL 10866/0007-0010

Nicobrand Limited
LAY SUMMARY

Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum
(nicotine resinate, medicated chewing gum, 2 mg and 4 mg)

This is a summary of the Public Assessment Report (PAR) for Nicotine Mint 2 mg Medicated Chewing Gum (PL 10866/0007), Nicotine Mint 4 mg Medicated Chewing Gum (PL 10866/0008), Nicotine Fruit 2 mg Medicated Chewing Gum (PL 10866/0009), Nicotine Fruit 4 mg Medicated Chewing Gum (PL 10866/0010). It explains how Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum.

For practical information about using Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum, patients should read the package leaflet or contact their doctor or pharmacist.

What are Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum and what are they used for?
Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum are medicines with ‘well established use’. This means that the medicinal use of the active substance nicotine (as resinate) is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

Nicotine belongs to a group of medicines which are used to help the patient stop smoking.

How do Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum work?
Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum contain the active ingredient nicotine. These medicines can be used to relieve the symptoms of nicotine withdrawal and to relieve and/or prevent the cravings for nicotine that the patient gets when the patient:

• stops smoking completely
• cuts down on the number of cigarettes they smoke while they are trying to give up
• feels unable to stop smoking but they don’t want to smoke cigarettes or the patient wants to avoid causing harm to others, such as when they are in a public place or are with friends and family.

When the patient stops smoking, cuts down, or is unable to smoke cigarettes, the patient’s body misses the nicotine they have been getting from the smoke. The patient may experience unpleasant feelings and a strong desire to smoke (“cravings”). Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum will help relieve and/or prevent the unpleasant withdrawal symptoms such as irritability, low mood, anxiety, restlessness and the patient’s craving to smoke.

The patient should always aim to stop smoking completely whilst using this medicine. To help the patient, they should also try to use a behavioural support programme to increase their chances of successfully stopping smoking.

The use of Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum is safer than smoking tobacco, but as soon as the patient is ready, they should aim to stop smoking completely.

How is Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum used?
The pharmaceutical form of Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum is a medicated chewing gum and the route of administration is oral.
Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment. Section 3 of the package leaflet includes the number of gums the patient should be using, when they should take them, how to take them and the maximum amount of time the patient should be using this medicine for. The number of medicated chewing gums that the patient uses each day will depend on how many cigarettes they smoked and how strong they were. The 2 mg strength gums should be used by people who smoke 20 or fewer cigarettes each day or by heavier smokers when they are cutting down the number and strength of the nicotine gums they are using. The 4 mg strength gums should be used by people who smoke more than 20 cigarettes per day.

The method of chewing the gum is NOT the same as that for ordinary chewing gum. The patient must use the “How to chew Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum” instructions contained in the package leaflet. This way of chewing ensures that the nicotine is correctly released from the gum.

The patient must use only one piece of gum at a time and must not use more than a total of 15 pieces of gum per day.

This medicine can only be obtained without a prescription and is on the general sales list (GSL) medicine.

What benefits of Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum have been shown in studies?
As nicotine is a well-known substance, and its use in the treatment of symptoms of nicotine withdrawal and to relieve and/or prevent the cravings for nicotine is well established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of the use of nicotine in the treatment of symptoms of nicotine withdrawal and to relieve and/or prevent the cravings for nicotine.

In addition, the company (Nicobrand Limited) undertook 2 bioequivalence studies to bridge their higher strength products (4 mg strength gum) to the information found in the bibliographic sources relating to the currently approved nicotine replacement therapy (NRT). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

It was concluded from these studies that Nicotine Mint/Fruit 4 mg Medicated Chewing Gum are comparable to another nicotine product already on the market, Nicorette Gum 4 mg.

What are the possible side effects of Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum?
The most common side effects with Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum (which may affect more than 1 in 10 people) are headache, hiccups, sore mouth and throat, stomach upsets, nausea and jaw-muscle ache.

For the full list of all side effects reported with Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum, see section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

Why were Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum approved?
The use of nicotine in the treatment of symptoms of nicotine withdrawal and to relieve and/or prevent the cravings for nicotine is well-established in medical practice and documented in the scientific literature. No new or unexpected safety concerns arose from these applications. It was, therefore, considered that the benefits of Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum outweigh the risks and the grant of marketing authorisations was recommended.
What measures are being taken to ensure the safe and effective use of Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum?
Safety information has been included in the Summary of Product Characteristics and the package leaflet for Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum
The marketing authorisations for Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum were granted on 26 November 2014.

The full PAR for Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum follows this summary.

For more information about use of Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in January 2015.
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I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Nicobrand Limited Marketing Authorisations for the medicinal products Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum (PL 10866/0007-0010) on 26 November 2014. The products are General Sales List (GSL) medicines indicated for the relief and/or prevention of craving and nicotine withdrawal symptoms associated with tobacco dependence. They are indicated to aid smokers wishing to quit or reduce prior to quitting, to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them. Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum should preferably be used in conjunction with a behavioural support programme.

These applications were submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be applications for a product containing an active substance of well-established use.

The pharmacological effects of nicotine are well documented. Those resulting from chewing Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum are comparatively small. The response at any one time represents a summation of stimulant and depressant actions from direct, reflex and chemical mediator influences on several organs. The main pharmacological actions are central stimulation and/or depression; transient hyperpnoea; peripheral vasoconstriction (usually associated with a rise in systolic pressure); suppression of appetite and stimulation of peristalsis.

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

Bibliographic data on nicotine have been submitted to support these applications. No new non-clinical studies were conducted for these applications, which is acceptable given that these are bibliographic applications for a product containing an active ingredient of well-established use.

In addition to the submission of published non-clinical and clinical references the applicant has also performed two bioequivalence studies (open-label, single-dose, randomised, three-way, cross-over studies) to bridge their 4 mg strength products to the information found in the bibliographic sources relating to a currently approved nicotine replacement product (NRT), Nicorette 4 mg Gum (GlaxoSmithKline). The applicant has stated that the bioequivalence studies were conducted in accordance with the guidelines set forth by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the U.S Code of Federal Regulations (21 CFR Part 50 and 56) and the Declaration of Helsinki regarding the treatment of human subjects in a study.

The MHRA has been assured that acceptable standards of Good Manufacturing Practise (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products.
II QUALITY ASPECTS

II.1 Introduction
Each medicated chewing gum contains 2 mg or 4 mg of nicotine (as nicotine resinate). Other ingredients consist of the pharmaceutical excipients:

Core
Gum base (containing butylhydroxytoluene [E321]), xylitol (E967), sodium carbonate, anhydrous, sodium hydrogen carbonate (E500), magnesium oxide (light), entrapped menthol flavour, levomenthol, toothpaste flavour and talc (E535b). In addition Nicotine Fruit 2 mg and 4 mg Medicated Chewing Gum also contains acesulfame potassium (E950), sucralose, Brown Lake (consisting of Sunset Yellow [E110], Allura Red [E129] and Indigo [E132])

Coating
Nicotine Mint 2 mg and 4 mg Medicated Chewing Gum:
Xylitol (E967), hydroxypropylcellulose, acacia, spray dried, acesulfame potassium (E950), titanium dioxide (E171), levomenthol, toothpaste flavour and carnauba wax (E903). The 4 mg strength also contains Sunset Yellow FCF (E110).

Nicotine Fruit 2 mg and 4 mg Medicated Chewing Gum:
Xylitol (E967), acacia, spray dried, acesulfame potassium (E950), titanium dioxide (E171), Brown Lake (consisting of Sunset Yellow [E110], Allura Red [E129] and Indigo [E132]), N & A Citrus/fruit flavour and carnauba wax (E903).

All strengths and flavours of the finished product are packed into polyvinyl chloride (PVC)/polyvinylidene chloride (PVdC)/aluminium blisters in blisters containing 10 pieces of gum in pack sizes of 40 and 100 gum pieces. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substance
INN: Nicotine resinate
Chemical name: Nicotine polacrilex Ph. Eur.

Structural formula:

\[
\text{Molecular formula: } C_{10}H_{14}N_2 \cdot (C_{18}H_{22}O_4)_n \\
\text{Appearance: } \text{A fine white powder} \\
\text{Solubility: } \text{Practically insoluble in solvents and water.}
\]

Nicotine resinate is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials 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.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, medicated gum containing 2 mg or 4 mg nicotine (as resinate) per piece of gum.

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the gum base, entrapped menthol flavour, toothpaste flavour, the colouring Brown Lake, Sunset Yellow (E110) and the flavouring N & A Citrus/Fruit flavour which are controlled to suitable in-house specifications and sucralose which is controlled in accordance with the National Formulary (NF) requirements. In addition, all colourings are stated to comply with EU approved specifications for colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

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

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

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of these products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and shown satisfactory results.

Finished Product Specifications
The finished product specifications proposed are acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with the storage conditions ‘Do not store above 25°C. Store in the original blister in order to protect from moisture. Keep the blister in the outer carton in order to protect from light.’
Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of these applications from a pharmaceutical viewpoint.

II.5 Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The following text is the approved label text for Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum. No label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained:
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Nicotine Mint 2mg Medicated Chewing Gum,

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Nicotine resinate

3. LIST OF EXCIPIENTS

Also contains gum base, (containing Butylhydroxytoluene (E321)), Xylitol(E967), Sodium carbonate anhydrous, Sodium hydrogen carbonate (E500), Magnesium oxide (light), Entrapped menthol flavour, Levomenthol. Toothpaste flavour, Talc(E553b).

Xylitol(E967), Hydroxypropylcellulose, Acacia spray-dried, Acesulfame potassium(E950), Titanium dioxide (E171), Levomenthol toothpaste flavor, Carnauba wax(E903).

4. PHARMACEUTICAL FORM AND CONTENTS

40 pieces of gum containing nicotine resinate

100 pieces of gum containing nicotine resinate

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Not Applicable

8. EXPIRY DATE

Exp.
9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Store in the original blister in order to protect from moisture. Keep the blister in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE.

To dispose of used gum, wrap in paper before putting into a waste bin.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Nicobrand Limited
189 Castlereoe Road
Coleraine BT51 3RP
Northern Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 10866/0007

13. MANUFACTURER'S BATCH NUMBER

B. N.

14. GENERAL CLASSIFICATION FOR SUPPLY

GSL

15. INSTRUCTIONS ON USE

Nicotine Mint 2 mg Medicated Chewing Gum is an aid to combat the withdrawal symptoms caused by giving up smoking.

Nicotine Mint 2 mg Medicated Chewing Gum is for smokers who smoke 20 or less cigarettes per day.

Instructions for use
For oral use only.
For adults and adolescents over 12 years of age. Read the enclosed instructions carefully before use.
You must not smoke whilst using these gums. This product is designed to be chewed, do not swallow. Chew 1 piece of gum using the chew and rest technique when you feel the urge to smoke.
Only use one piece of gum at the time and do not use more than 15 pieces of gum a day.
Chew and rest technique
Chew slowly until taste becomes strong.
Rest between gum and cheek.
Chew again when taste has faded.

Warnings and Precautions for Use
Do not use if you are:
• a non-smoker or an occasional smoker
• allergic to any of the ingredients
• under 12 years of age

Consult your doctor, nurse or pharmacist before starting to use these gums if you are:
• in hospital with serious heart disease
• pregnant or breast-feeding
• under a doctor's care or taking prescribed medication

Do not exceed the stated dose

To remove the gum, Tear off single unit
Peel off backing starting at corner with loose edge.
Push gum through foil.

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

Stop Smoking Aid
For smokers who smoke less than 20 cigarettes a day

Sugar Free

16. INFORMATION IN BRAILLE

Nicotine Mint 2mg Medicated Chewing Gum
<table>
<thead>
<tr>
<th><strong>MINIMUM PARTICULARS TO APPEAR ON BLISTERS</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Blisters Foil</strong></td>
</tr>
<tr>
<td>1. <strong>NAME OF THE MEDICINAL PRODUCT</strong></td>
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<tr>
<td>Nicotine Mint 2mg Medicated Chewing Gum</td>
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<tr>
<td>2. <strong>NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
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<tr>
<td>Nicobrand Limited</td>
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<tr>
<td>3. <strong>EXPIRY DATE</strong></td>
</tr>
<tr>
<td>Exp.:</td>
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<tr>
<td>4. <strong>BATCH NUMBER</strong></td>
</tr>
<tr>
<td>B.N.</td>
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</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Nicotine Mint 4mg Medicated Chewing Gum,

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Nicotine resinate

3. LIST OF EXCIPIENTS

Also contains Gum base, (containing Butylhydroxytoluene (E321)), Xylitol (E967), Sodium carbonate anhydrous, Sodium hydrogen carbonate (E500), Magnesium oxide (light), Entrapped menthol flavour, Levomenthol, Toothpaste flavour, Talc(E553b)

Xylitol(E967), Hydroxypropylcellulose, Acacia spray-dried, Acesulfame potassium(E950), Titanium dioxide(E171), Levomenthol toothpaste flavor, Carnauba wax(E903), Sunset Yellow FCF (E110)

4. PHARMACEUTICAL FORM AND CONTENTS

40 pieces of gum containing nicotine resinate
100 pieces of gum containing nicotine resinate

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Not Applicable

8. EXPIRY DATE
9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Store in the original blister in order to protect from moisture. Keep the blister in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE.

To dispose of used gum, wrap in paper before putting into a waste bin.

11. NAME AND ADDRESS OF THE MARKETING AUTHORITY

Nicobrand Limited
189 Castleroe Road
Coleraine BT51 3RP
Northern Ireland

12. MARKETING AUTHORITY NUMBER(S)

PL 10866/0008

13. MANUFACTURER'S BATCH NUMBER

B. N.

14. GENERAL CLASSIFICATION FOR SUPPLY

GSL

15. INSTRUCTIONS ON USE

Nicotine Mint 4 mg Medicated Chewing Gum is an aid to combat the withdrawal symptoms caused by giving up smoking.

Nicotine Mint 4 mg Medicated Chewing Gum is for smokers who smoke more than 20 cigarettes per day. If you smoke 20 or less cigarettes per day, you should use Nicotine 2 mg Medicated Gum.

Instructions for use
For oral use only.
For adults and adolescents over 12 years of age.
Read the enclosed instructions carefully before use.
You must not smoke whilst using these gums.
This product is designed to be chewed, do not
swallow. Chew 1 piece of gum using the chew and rest technique when you feel the
urge to smoke.
Only use one piece of gum at the time and do not use more than 15 pieces of gum a day.

Chew and rest technique
Chew slowly until taste becomes strong.
Rest between gum and cheek.
Chew again when taste has faded.

Warnings and Precautions for Use
Do not use if you are:
• a non smoker or an occasional smoker
• allergic to any of the ingredients
• under 12 years of age

Consult your doctor, nurse or pharmacist
before starting to use these gums if you are:
• in hospital with serious heart disease
• pregnant or breast-feeding
• under a doctor’s care or taking prescribed
  Medications

Do not exceed the stated dose

To remove the gum,
Tear off single unit.

Peel off backing
starting at corner
with loose edge.

Push gum through foil.

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

Stop Smoking Aid
For smokers who smoke more
than 20 cigarettes a day

Sugar Free

16. INFORMATION IN BRAILLE

Nicotine Mint 4mg Medicated Chewing Gum
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Carton**

1. **NAME OF THE MEDICINAL PRODUCT**

Nicotine Fruit 2mg Medicated Chewing Gum

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Nicotine resinate

3. **LIST OF EXCIPIENTS**

*Also contains Gum base, (containing Butylhydroxytoluene (E321)), Xylitol (E967), Sodium carbonate anhydrous, Sodium hydrogen carbonate (E500), Magnesium oxide (light), Entrapped menthol flavour, Acesulfame potassium, Sucrose, Brown Lake (E110 Sunset Yellow, E129 Allura Red and E132 Indigo), Toothpaste flavour, Levomenthol, Talc(E553b)*

Xylitol (E967), Acacia, spray-dried, Acesulfame potassium (E950), Titanium dioxide (E171), brown lake (E110 Sunset Yellow, E129 Allura Red and E132 Indigo), and N&A citrus fruit flavor, Carnauba wax (E903).

See leaflet for further information

4. **PHARMACEUTICAL FORM AND CONTENTS**

40 pieces of gum containing nicotine resinate

100 pieces of gum containing nicotine resinate

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For oral use only.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the sight and reach of children

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

Not Applicable

8. **EXPIRY DATE**
9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Store in the original blister in order to protect from moisture. Keep the blister in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE.

To dispose of used gum, wrap in paper before putting into a waste bin.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Nicobrand Limited
189 Castlereagh Road
Coleraine BT51 3RP
Northern Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 10866/0009

13. MANUFACTURER’S BATCH NUMBER

B. N.

14. GENERAL CLASSIFICATION FOR SUPPLY

GSL

15. INSTRUCTIONS ON USE

Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum is an aid to combat the withdrawal symptoms caused by giving up smoking.
Nicotine Fruit 2 mg Medicated Chewing Gum is for smokers who smoke 20 or less 20 cigarettes per day.

Instructions for use
For oral use only.
For adults and adolescents over 12 years of age.
Read the enclosed instructions carefully before use.
You must not smoke whilst using these gums. This product is
designed to be chewed, do not swallow. Chew 1 piece of gum using the chew and rest technique when you feel the urge to smoke. Only use one piece of gum at the time and do not use more than 15 pieces of gum a day.

Chew and rest technique
Chew slowly until taste becomes strong.
Rest between gum and cheek.
Chew again when taste has faded.

Warnings and Precautions for Use
Do not use if you are:
• a non-smoker or an occasional smoker
• allergic to any of the ingredients
• under 12 years of age

Consult your doctor, nurse or pharmacist before starting to use these gums if you are:
• in hospital with serious heart disease
• pregnant or breast-feeding
• under a doctor’s care or taking prescribed medication

Do not exceed the stated dose

To remove the gum, tear off single unit. Peel off backing starting at corner with loose edge. Push gum through foil.

Stop Smoking Aid
For smokers who smoke less than 20 cigarettes a day

Sugar Free

16. INFORMATION IN BRAILLE

Nicotine Fruit 2mg Medicated Chewing Gum
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Nicotine Fruit 4mg Medicated Chewing Gum,

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Nicotine resinate

3. LIST OF EXCIPIENTS

Also contains Gum base, (containing Butylhydroxytoluene (E321)), Xylitol (E967), Sodium carbonate anhydrous, Sodium hydrogen carbonate (E500), Magnesium oxide (light), Entrapped menthol flavour, Acesulfame potassium, Sucralose, Brown lake (E110 Sunset Yellow; E129 Allura Red and E132 Indigo), Toothpaste flavour, Levomenthol, Talc (E553b)

Xylitol (E967), Acacia spray-dried, Acesulfame potassium (E950), Titanium dioxide (E171), Sunset Yellow (E110), Brown lake (E110 Sunset Yellow, E129 Allura Red and E132 Indigo), and N&A citrus fruit flavor. Carnauba wax (E903)

4. PHARMACEUTICAL FORM AND CONTENTS

40 pieces of gum containing nicotine resinate

6. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Not Applicable
8. EXPIRY DATE

Exp.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Store in the original blister in order to protect from moisture. Keep the blister in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE.

To dispose of used gum, wrap in paper before putting into a waste bin.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Nicobrand Limited
189 Castleroe Road
Coleraine BT51 3RP
Northern Ireland

12. MARKETING AUTHORISATION NUMBER(S)

PL 10866/0010

13. MANUFACTURER’S BATCH NUMBER

B. N.

14. GENERAL CLASSIFICATION FOR SUPPLY

GSL

15. INSTRUCTIONS ON USE

Nicotine 4 mg Medicated Chewing Gum is an aid to combat the withdrawal symptoms caused by giving up smoking.

Nicotine 4 mg Medicated Chewing Gum is for smokers who smoke more than 20 cigarettes per day. If you smoke 20 or less cigarettes per day, you should use Nicotine 2mg Medicated Gum

Instructions for use
For oral use only.
For adults and adolescents over 12 years of age.
Read the enclosed instructions carefully before use.
You must not smoke whilst using these gums.
This product is designed to be chewed, do not
swallow. Chew 1 piece of gum using the chew and rest technique when you feel the
urge to smoke.

Only use one piece of gum at the time and do not use more than 15 pieces of gum a day.

Chew and rest technique
Chew slowly until taste becomes strong.
Rest between gum and cheek.
Chew again when taste has faded.

Warnings and Precautions for Use
Do not use if you are:
• a non smoker or an occasional smoker
• allergic to any of the ingredients
• under 12 years of age

Consult your doctor, nurse or pharmacist
before starting to use these gums if you are:
• in hospital with serious heart disease
• pregnant or breast-feeding
• under a doctor’s care or taking prescribed
Medication

Do not exceed the stated dose

To remove the gum,
Tear off single unit.

Peel off backing
starting at corner
with loose edge.

Push gum through foil.

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

Stop Smoking Aid
For smokers who smoke more
than 20 cigarettes a day

Sugar Free

16. INFORMATION IN BRAILLE

Nicotine Fruit 4mg Medicated Chewing Gum
III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of nicotine are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Nicotine Mint/Fruit 2 mg and 4 mg Medicated Chewing Gum will not be administered at a higher dosage level, for a longer duration or for different indications than were previously in effect this will not lead to an increased exposure to the environment, in addition, nicotine is unlikely to result in significant risk to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that these are bibliographic applications for a product containing an active ingredient of well-established use

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction
Two bioequivalence studies were submitted to support these applications. The studies were designed to demonstrate that achieved blood plasma levels of nicotine from the formulations are consistent with safe and efficacious therapeutic levels for an existing reference NRT product on the market (Nicorette 4 mg Gum [GlaxoSmithKline]).

With the exception of the two bioequivalence studies, no new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and information on the safety of nicotine.

The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
The applicant has submitted the following two studies:
**STUDY 1**
An open label, randomised, three-way, cross-over study to compare the systemic exposure of nicotine following a single dose of the test product Nicotine Fruit 4 mg Medicated Chewing Gum (Nicobrand Limited) versus the reference product, Nicorette 4 mg Gum (GlaxoSmithKline) in healthy, adult smoker volunteers.

Subjects received a single dose of either the test or reference product following a fast of at least 10 hours. The gum was chewed three times every four seconds. There was neither swallowing of the gum nor blowing of bubbles. The rhythm of chewing was provided by a timer with an audible signal.

While seated, the subjects chewed the gum three times on one side of the mouth then moved it to the other side of the mouth. Every four seconds, the tone sounded prompting the subjects to chew three times on the opposite side from the previous chew. The subjects were instructed to swallow at a verbal command given every 30 seconds. Each treatment period included a total of one chewing session 30 minutes in duration.

Blood samples were collected before and up to and including 16 hours post-dose. The washout period between treatment phases was 7 days. The pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Reference</th>
<th>% Ratio</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-t} (ng·hr/mL)</td>
<td>27.66</td>
<td>31.81</td>
<td>86.96</td>
<td>(83.37, 90.69)</td>
</tr>
<tr>
<td>AUC_{0-∞} (ng·hr/mL)</td>
<td>29.75</td>
<td>33.95</td>
<td>87.63</td>
<td>(84.27, 91.12)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>8.29</td>
<td>9.78</td>
<td>84.78</td>
<td>(80.95, 88.79)</td>
</tr>
</tbody>
</table>

AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from zero to t hours
C_{max} maximum plasma concentration

**STUDY 2**
An open label, randomised, three-way, cross-over study to compare the systemic exposure of nicotine following a single dose of the test product Nicotine Mint 4 mg Medicated Chewing Gum (Nicobrand Limited) versus the reference product, Nicorette 4 mg Gum (GlaxoSmithKline) in healthy, adult smoker volunteers.

Subjects received a single dose of either the test or reference product following a fast of at least 10 hours. The gum was chewed three times every four seconds. There was neither swallowing of the gum nor blowing of bubbles. The rhythm of chewing was provided by a timer with an audible signal.

While seated, the subjects chewed the gum three times on one side of the mouth then moved it to the other side of the mouth. Every four seconds, the tone sounded prompting the subjects to chew three times on the opposite side from the previous chew. The subjects were instructed to swallow at a verbal command given every 30 seconds. Each treatment period included a total of one chewing session 30 minutes in duration.

Blood samples were collected before and up to and including 16 hours post-dose. The washout period between treatment phases was 7 days. The pharmacokinetic results are presented below:
From the data provided, it is accepted that the test products Nicotine Fruit 4 mg Medicated Chewing Gum and Nicotine Mint 4 mg Medicated Chewing Gum are both bioequivalent to the reference product Nicorette 4 mg Gum (GlaxoSmithKline). Therefore the clinical data for the already approved Nicorette 4 mg gums are directly applicable to the applicant’s Nicotine Mint/Fruit 4 mg Medicated Chewing Gum with regard to efficacy and bridging is accepted.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for applications of this type. The clinical efficacy of nicotine is well-established. Efficacy is adequately reviewed in the clinical overview.

IV.5 Clinical safety
No new safety data were submitted and none were required for these bibliographic applications. Safety is adequately reviewed in the clinical overview. The safety profile of nicotine is well-known.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance system
The applicant has provided a suitable justification for the non-submission of a Risk Management Plan (RMP). These applications were submitted prior to 21 July 2012 (the date when the requirement for the submission of RMPs for all initial marketing authorisation (MA) applications came into effect).

The applicant has provided details of a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that they have access to the services of a qualified person responsible for pharmacovigilance, and have the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.
IV.7  Discussion on the clinical aspects
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

The bibliographic data submitted for these applications does support the claim of well-established use for the sought indication of:
‘The relief and/or prevention of craving and nicotine withdrawal symptoms associated with tobacco dependence. They are indicated to aid smokers wishing to quit or reduce prior to quitting, to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them’ in the target population.

The applicant has also performed two bioequivalence studies effectively bridging Nicotine Mint/Fruit 4 mg Medicated Chewing Gum to the information found in the bibliographic sources relating to the currently approved Nicorette 4 mg Gum (GlaxoSmithKline).

The grant of marketing authorisations is recommended for these applications.

V  User consultation
The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability, as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

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