CBG MEB

# PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

## Nicorette Menthol Mint 2 mg and 4 mg, medicated chewing-gum
## Johnson & Johnson Consumer B.V., the Netherlands

## nicotine

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**Registration number in the Netherlands: RVG 104193-104194**

**20 March 2013**

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|---|---|
| Pharmacotherapeutic group: | drugs used in nicotine dependence |
| ATC code: | N07BA01 |
| Route of administration: | oromucosal |
| Therapeutic indication: | relief of (severe) nicotine withdrawal symptoms in smoking cessation |
| Prescription status: | non prescription |
| Date of authorisation in NL: | 29 March 2012 |
| Application type/legal basis: | Directive 2001/83/EC, Article 8(3) |

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

# I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Nicorette Menthol Mint 2 mg and 4 mg, medicated chewing-gum from Johnson & Johnson Consumer B.V. The date of authorisation was on 29 March 2012 in the Netherlands.

The product is indicated for relief of (severe) nicotine withdrawal symptoms in smoking cessation.

Nicorette Menthol Mint may also be used as part of a smoking reduction strategy as a step towards stopping completely.

A comprehensive description of the indications and posology is given in the SPC.

Nicotine has no therapeutic uses except as replacement therapy for the relief of abstinence symptoms in nicotine-dependent smokers.
Owing to its many actions, the overall effects of nicotine are complex. A wide variety of stimulant and depressant effects are observed that involve the central and peripheral nervous, cardiovascular, endocrine, gastro-intestinal and skeletal motor systems. Nicotine acts on specific binding sites or receptors throughout the nervous system.

Abrupt cessation of the use of tobacco-containing products following a prolonged period of daily use results in a characteristic withdrawal syndrome that includes four or more of the following: dysphoria or depressed mood; insomnia; irritability; frustration or anger; anxiety; difficulty concentrating, restlessness or impatience; decreased heart rate; and increased appetite or weight gain. Nicotine craving, which is recognised as a clinically relevant symptom, is also an important element in nicotine withdrawal.
Clinical studies have shown that nicotine replacement from nicotine containing products can help people give up smoking by relief of abstinence symptoms associated with smoking cessation.

This national procedure concerns line extension to Nicorette Freshmint 2 mg and 4 mg medicated chewing-gum (NL License RVG 31524 and 31525), which have been registered in the Netherlands since 8 April 2005. The composition of the core of the new gum (containing whitening substances) is exactly the same as the established taste variant Freshmint, in qualitative and quantitative respect. The only difference is that the new form contains an extra outer layer of menthol flavour.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

This national procedure concerns a so-called full dossier application according to Article 8(3) of Directive 2001/83/EC, a dossier with administrative, chemical-pharmaceutical, pre-clinical and clinical data.
The active component of Nicorette Menthol Mint is considered to be well-known and the clinical pharmacology of nicotine has been extensively studied. Parts of the data in the dossier were already submitted in the dossier of Nicorette Freshmint. With the application at issue, the MAH applied for an additional claim in section 4.2 of the SPC regarding a teeth whitening effect of the excipients anhydrous sodium carbonate, sodium hydrogen carbonate and xylitol.
To support the whitening claim, the MAH submitted data from a randomised trial (Study A85), where the Innovator Nicorette *Freshmint gum* was compared to regular nicotine sublingual *tablets* in a 12 weeks treatment period. The results of the study are discussed in section II.3 ‘Clinical aspects’.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a line extension.

# II SCIENTIFIC OVERVIEW AND DISCUSSION

## II.1 Quality aspects

**Compliance with Good Manufacturing Practice**
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

**Active substance**
The active substance is nicotine resinate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white to faintly yellowish fine powder, which is practically insoluble in water. Nicotine has one chiral centre and is produced as the S-(-)-isomer.
Initially full documentation on the active substance was included in the dossier; post approval the CEP procedure was adopted.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and CEP specifications. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 batches of each supplier.

Stability of drug substance
For one active substance manufacturer a retest period of not more than 30 months is applicable when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.
For the other CEP holder the approved retest period is not more than 36 months. This was also granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

**Medicinal Product**

Composition
Nicorette Menthol Mint 2 mg and 4 mg medicated chewing-gums contain 10 mg and 20 mg nicotine resinate respectively, corresponding to 2 mg and 4 mg of nicotine.
The gums have a square form; the 2 mg strength is white and the 4 mg is cream coloured.

The medicated chewing-gum is packed in blisters out of Al/PVC-PVDC-blisters.

The excipients are: chewing gum base, xylitol, peppermint oil, anhydrous sodium carbonate, sodium hydrogen carbonate (only 2 mg formulation), acesulfame potassium, levomenthol, light magnesium oxide, quinoline yellow (only 4 mg formulation), aromas, hypromellose, sucralose, polysorbate 80, pregelatinized starch, titanium dioxide, talc and carnauba wax.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The applied overage is justified. The formulation is based on the existing Nicorette Freshmint 2 mg and 4 mg medicated chewing-gums. The *in vitro* release profile of the Nicorette Menthol Mint 2 mg and 4 mg and Nicorette Freshmint 2 mg and 4 mg have been investigated on 3 batches per formulation (6 individual gums per batch). Results show a nicotine release of about 80% after 10 minutes and about 100% after 30 minutes. The *in vitro* nicotine release profiles of the two formulations were shown to be comparable (supported by calculations of the similarity factor in accordance with the 'Note for Guidance on Investigation of Bioavailability and Bioequivalence'). The gum cores of the Menthol Mint and Freshmint formulations are similar, only the coating is different. The *in vitro* data shows that nicotine release is not affected by the difference in coating. It is therefore considered to be unlikely that the different coating has a negative effect on the *in vivo* bioavailability.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of mixing step, forming, coating and a packaging. The manufacture of the gum cores was fully validated for the Nicorette Freshmint 2 mg and 4 mg medicated chewing-gum. The coating process has been validated on 3 pilot-scale batches. Process validation of the coating process for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with the Ph.Eur., USP/NF or in-house specifications. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, assay, related substances, uniformity of dosage units and microbiological quality. Except for assay the release and shelf-life limits are identical. The specifications are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 pilot-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided 3 pilot-scale batches per strength stored at 25°C/60% RH (24 months), 30°C/65% RH (6 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al/PVC-PVDC-blisters. Under accelerated and intermediate conditions a slight increase of total impurities is observed. However, under all conditions, the tested parameters comply with the specification. Photostability studies were performed in accordance with the 'Guideline on Photostability Testing'. The product is sensitive to light. The proposed shelf-life of 36 months and storage condition 'Keep the blister in the outer carton in order to protect from light' are justified. Results from the ongoing stability study will be finalized throughout the shelf-life of 24 months and reported at the end of shelf life.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

## II.2 Non-clinical aspects

This product is a line extension to Nicorette Freshmint medicated chewing-gum, which is available on the European market. No new preclinical data have been submitted. The MAH referred to the preclinical documentation included in the Freshmint application. Therefore the application has not undergone additional preclinical assessment. This is acceptable for this type of application.

**Environmental risk assessment**

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of nicotine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

## II.3 Clinical aspects

Nicotine is a well-known active substance with established efficacy and tolerability. With regard to clinical aspects, reference is made to the Nicorette Freshmint dossier. However, for the Menthol Mint product the MAH applied for an additional claim, a teeth whitening effect. In support of this claim, data from a randomised trial (Study A85) were submitted; a study in which the Innovator Nicorette *Freshmint* gum was compared to regular nicotine *sublingual tablets* in a 12 weeks treatment period (N=200).

**Study A85**
*Design*
An evaluator-blinded, randomized, 12-week parallel-group controlled trial was conducted among 200 daily smokers motivated to quit smoking. No placebo arm was added. Primary outcome was change of tooth colour from baseline by the Lobene Stain Index (modified by MacPherson), between baseline and 6 weeks. The Lobene index is a mean stain score of 8 incisor teeth, taking intensity and area into account (maximum score 9). Secondary outcome was quit rate.
Doses varied from 2-4 mg, depending on the prior smoking status of the subjects. In addition, data of a short-term exploratory open-label study without comparator (Study A88) and an *in-vitro* study evaluating whitening properties of different ingredients were submitted as supportive evidence.

*Results*
At Week 6, the mean total stain index was marginally lower in the gum-group compared to baseline (delta -0.15 (4.16 to 4.01), p=0.018). In the tablet-group the mean total stain index at Week 6 was higher than at baseline (4.31 to 4.42). The difference from baseline between gum versus tablet was statistically significant (p=0.005) in favor of the gum. However, at longer tem at week 12, the differences between gum and tablets regarding teeth whitening were not significant anymore (delta -0.07 and -0.05 respectively). The decline in staining in the tablet arm between week 6-12 weeks might be due to smoking abstinence.

Drop-out rates were similar for both study arms (about 50%). Smoking abstinence rates were similar for the new gum formulation (35%) and the active comparator (tablets) (38%). The most common treatment-related adverse events were gastrointestinal disorders like nausea (reported by 21.6% of gum and 36.7% of tablet users).

The composition of the core of the Menthol Mint gum is exactly the same as the established taste variant Freshmint, in qualitative and quantitative respect. The only difference is that the Menthol Mint form contains an extra outer layer of menthol flavour. Dissolution profiles of both Freshmint and Menthol Mint flavour are similar (>90% at 20 min, in an artificial chewing setting). Therefore the clinical data from the Freshmint study can be extrapolated to the new Menthol Mint form, as dissolution is similar and the composition of the core of the gum identical.

**Benefit/risk assessment**
The line extension with Menthol Mint flavouring is approvable, as broadening the treatment armentarium by adding different flavours may be of interest for the consumer.
However, the additional claim regarding whitening cannot be included in section 4.2 of the SPC, as the whitening effect is clinically irrelevant: the effect is very small, and not persistent. After twelve weeks, the regular treatment period, no differences were observed between the gum and the sublingual tablet.
The patients were aware of the possible whitening effect of the gum. However, this did not lead to a greater motivation or success rate to quit smoking.
Moreover, the improvements in stain that occurred with Freshmint gum in the first 6 weeks were primarily due to reductions in staining on the lingual surfaces, but not on the facial surfaces of the teeth. However, whitening of the optical visible facial surface may be more relevant for the users than the not directly visible lingual site.

The qualitative and quantitative composition of this product is not different from marketed nicotine gum, except for the taste. Therefore, there is no basis for additional claims for Nicorette Menthol Mint specifically.
In conclusion, the benefit/risk profile for the line extension with the Menthol Mint flavouring is positive. However a claim regarding teeth whitening effects is insufficiently supported by clinical data and can therefore not be approved for inclusion in section 4.2 of the SPC.

Risk management plan
The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks. The safety profile of Nicorette Menthol Mint is expected to be similar to that of Nicorette Freshmint. No additional risk management activities are considered necessary.

**Product information**

SPC
The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product Nicorette Freshmint medicated chewing-gum.

Readability test
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. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The results of the pilot round were satisfactory; no major changes were made to the PL. The final version of the leaflet was approved by the readers, since all question reached the 90%/90% threshold. The total score for the second group was significantly higher than the score for the first group, meaning that the changes made to the leaflet after phase one had a positive effect. The readability test has been sufficiently performed.

## III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Nicorette Menthol Mint 2 mg and 4 mg, medicated chewing-gums have a proven chemical-pharmaceutical quality and are approvable line extensions to Nicorette Freshmint. Nicorette Freshmint is a well-known medicinal product with an established favourable efficacy and safety profile.

The MAH proposed to include an additional claim regarding teeth whitening in section 4.2 of the SPC. This claim was based on the results of study A85, in which the teeth whitening effect of Nicorette Freshmint gum was investigated in comparison to nicotine sublingual tablets. However**,** the observed whitening effect is clinically not relevant: the effect is very small, and certainly not persistent. Therefore, inclusion of a whitening claim in the SPC was not approved.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of Nicorette Freshmint. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Nicorette Menthol Mint 2 mg and 4 mg, medicated chewing-gum were authorised in the Netherlands on 29 March 2012.

There following post-approval commitment was made during the procedure.

<u>Quality – medicinal product</u>

- The MAH committed to finalize the stability studies throughout the proposed shelf-life of 24 months and report results at the end of shelf life. This commitment has been fulfilled.

## List of abbreviations

| | |
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| ASMF | Active Substance Master File |
| ATC | Anatomical Therapeutic Chemical classification |
| AUC | Area Under the Curve |
| BP | British Pharmacopoeia |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence Interval |
| $C_{max}$ | Maximum plasma concentration |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CV | Coefficient of Variation |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EU | European Union |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| MEB | Medicines Evaluation Board in the Netherlands |
| OTC | Over The Counter (to be supplied without prescription) |
| PAR | Public Assessment Report |
| Ph.Eur. | European Pharmacopoeia |
| PIL | Package Leaflet |
| PSUR | Periodic Safety Update Report |
| SD | Standard Deviation |
| SPC | Summary of Product Characteristics |
| $t_{½}$ | Half-life |
| $t_{max}$ | Time for maximum concentration |
| TSE | Transmissible Spongiform Encephalopathy |
| USP | Pharmacopoeia in the United States |

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Scope | Procedure number | Type of modification | Date of start of the procedure | Date of end of the procedure | Approval/ non approval | Assessment report attached |
|---|---|---|---|---|---|---|
| Change in immediate packaging of the finished product | -- | IA | 11-5-2012 | 13-6-2012 | Approval | N |
| Deletion of manufacturing site for an active substance. | -- | IA | 11-5-2012 | 14-6-2012 | Approval | N |
| Submission of a new Ph. Eur. certificate of suitability: for an active substance: EP Certificate of Suitability to the relevant Ph. Eur. Monograph : New certificate from 2 new manufacturers. | -- | IA | 11-5-2012 | 16-5-2012 | Approval | N |
| Change in the storage conditions of the finished product. 'Store below 25°C' was deleted. | -- | IB | 11-5-2012 | 3-7-2012 | Approval | N |