CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Nicorette Inhaler 15 mg, inhalation vapour, liquid
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 111209

16 December 2013

Pharmacotherapeutic group:	drugs used in nicotine dependence
ATC code:	N07BA01
Route of administration:	inhalation
Therapeutic indication:	relief or treatment of severe nicotine withdrawal symptoms in smoking cessation
Prescription status:	non prescription
Date of authorisation in NL:	11 December 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 (SmPC), 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 Inhaler 15 mg, inhalation vapour, liquid from Johnson & Johnson Consumer B.V. The date of authorisation was on 11 December 2012 in the Netherlands.

The product is indicated for relief or treatment of severe nicotine withdrawal symptoms in smoking cessation.

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

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 a line extension to Nicorette Inhaler 10 mg, inhalation vapour, liquid (NL License RVG 18113), which has been registered by Johnson & Johnson Consumer B.V. since 25 July 1996. For this product a Public Assessment Report is available on the MEB website. The only difference of the new form versus the original inhaler is the strength.
The rationale for developing the Nicotine Inhaler 15 mg was to produce an inhaler cartridge that is bioequivalent with the 10 mg inhaler cartridge, but can be used for a twice as long period compared to the 10 mg cartridge. The aim is to simplify usage of the inhaler, by reducing the number of cartridges needed during a quit attempt. Nicotine Inhaler 15 mg is aimed at all smokers.

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 Inhaler 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 Inhaler 10 mg. To support the application at issue, the MAH submitted two bioequivalence studies in which the exposure to nicotine was measured after inhalation with the 10 mg inhaler and the new 15 mg inhaler, in two different replacement regimens of the cartridges. Also the exposure after use of the inhaler was compared with regular smoking. The results 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, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a clear, colourless or pale yellow liquid. It is volatile, hygroscopic, alkaline, soluble in water and miscible with ethanol.

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
A CEP has 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 the CEP with additional requirements on residual solvents, arsenic and heavy metals. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 batches.

Stability of drug substance
The active substance is stable for 4 years if stored below 25°C under the stated conditions. Assessment thereof was part of granting the CEP and has been 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 Inhaler 15 mg consists of a porous plug of polyethylene, serving as a reservoir for nicotine. The porous plug, loaded with 15 mg nicotine, is inserted in a sealed, transparent, plastic tube containing nitrogen as a protection gas against degradation. Nicotine vapor is released from the plug when a stream of air is allowed to pass through it. Nicotine is inhaled by means of a mouthpiece. The delivered amount of nicotine from the Nicotine Inhaler 15 mg is 7 mg when 24 liters of air has passed through the nicotine loaded porous plug which corresponds to the use of Nicotine Inhaler 15 mg for about 7 sessions. The pharmaceutical dosage form is inhalation vapour, liquid. The package sizes are 4 cartridges (start kit) and 20 cartridges (follow up kit).

The excipients are: levomenthol, and nitrogen, porous plug of polyethylene. Levomenthol is used as a flavouring agent.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. Development work for Nicotine Inhaler 15 mg is based on the experiences of Nicotine Inhaler 10 mg and the development of the 15 mg formulation has been focused on the same *in vitro* and *in vivo* release investigations. The inhaler unit conforms to the acceptance limits for uniformity of delivered dose in Ph.Eur. 'Preparations for Inhalation, Inhalanda', and mean delivered dose in the EMA guideline on the pharmaceutical quality of inhalation and nasal products (Doc. Ref EMEA/CHMP/QWP/49313/2005 Corr.). The same mouthpiece is used as for the Nicotine Inhaler 10 mg. The applied overage is justified by results of validation of the full-scale manufacturing process. The suitability of the container closure system has been shown in the stability studies that have been performed. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of mixing the drug substance with the excipients and then loading the plugs with the nicotine solution. The plugs are placed in the plastic tubes. The tubes are sealed and packed into trays.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three commercial-scale batches.

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

Container closure system
The Nicotine Inhaler 15 mg container closure system consists of plastic tube, in which the nicotine loaded plug is inserted; the tube is sealed at both ends by a foil. When the unit (cartridge) is placed into a mouthpiece, both seals are penetrated allowing air to pass through it. The product is ready for use. The user then draws air through the porous plug, which releases nicotine to the air stream. Each inhalation session will take 10 to 20 minutes. The mouthpiece is made of polypropylene. The packaging materials comply with relevant guidelines.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, degradation products, residual solvent, uniformity of delivered dose, mean delivered dose, and microbiological quality. With the exception of the limit for the assay, the release and end of shelf-life limits are identical. The acceptance criteria are considered acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided for three pilot-scale end three commercial-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three pilot-scale batches stored at 25°C/60%RH (36 months), 30°/65%RH (12 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 the commercial packaging material. No changes were observed for all three storage conditions. The proposed shelf-life of the drug product of 3 years, without temperature restrictions, is considered acceptable.
In-use stability data has been provided demonstrating that the product remains stable for 48 hours following placing the tube into the mouthpiece.

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 Inhaler 10 mg, which is available on the European market. No new preclinical data have been submitted. The MAH referred to the preclinical documentation included in the previous application. Therefore the application has not undergone additional preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
In accordance with the Q&A on the guideline for Environmental Risk Assessment, the MAH provided an adequate justification for the absence of specific study data. With the approval of this line extension no significant increase in environmental exposure is expected.

II.3 Clinical aspects

The concept of Nicorette Inhaler 10 or 15 mg is nicotine replacement therapy (NRT) by delivering nicotine via oral inhalation. The rationale for developing the Nicotine Inhaler 15 mg was to reduce the number of cartridges needed during a quit attempt compared to the 10 mg inhaler. No efficacy and safety studies are available for the 15 mg device. A direct waiver to the 10 mg dossier was challenged, considering that the dose is maintained longer for the 15 mg inhaler at repeat use, compared to the 10 mg. However, no significant accumulation is expected, even if patients would refill the inhaler-device with a 15 mg cartridge as frequently as they would normally do with the 10 mg cartridges.

For this line extension the MAH submitted two bioequivalence studies with different administration regimens and a pharmacokinetic study in which the nicotine level after use of the 15 mg inhaler is compared with regular smoking.

Pharmacokinetic study
Design
This study was conducted to determine the degree of substitution with the 15 mg inhaler as compared to cigarettes when used with the same technique as smoking a cigarette but during a time period 8 times longer.

In this study 21 subjects, smoking at least 15 cigarettes each day were included. The study design was two-way cross-over, multiple dose study. The subjects used the inhaler every hour for 11 hours (12 administrations), each inhalation session varying between 28 and 48 minutes. The nicotine cartridge was weighted together with the inhaler before the start of administration and after each administration to estimate the amount of nicotine extracted.
As reference the subjects smoked their preferred brand in their usual way of smoking, one cigarette every hour. Between the sessions a minimum of 4 days passed.
Besides the exposure comparison between the inhaler and cigarettes, the craving and satisfaction were estimated by questionnaires.

Blood samples were taken before each administration (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours).
In plasma nicotine was determined with a GC method with a nitrogen sensitive detector with a limit of quantitation of 0.5 g/ml.

Results
Exposure
The duration of smoking during the study varied between 2.33 and 6.77 minutes. The mean amount of nicotine extracted from the inhaler is given in the table and figure below:

Table 1. Extracted dose of nicotine in mg from the 15 mg nicotine inhaler, n=21.

Adm. No.	Mean ± S.D.	Median	Range	95% CI	P*
1	1.27 ± 0.97	0.91	0.23 - 3.96	0.83 – 1.71	-
2	1.08 ± 0.75	0.93	0.08 – 3.22	0.74 – 1.42	0.056
3	1.32 ± 0.66	1.19	0.42 - 2.54	1.01 – 1.62	0.008
4	1.01 ± 0.68	0.76	0.08 - 2.71	0.70 – 1.32	0.006
5	1.12 ± 0.62	1.02	0.25 - 2.71	0.83 – 1.40	0.393
6	1.07 ± 0.56	0.85	0.17 – 2.12	0.81 – 1.32	0.588
7	0.95 ± 0.44	0.85	0.17 – 2.12	0.75 – 1.15	0.667
8	0.70 ± 0.35	0.68	0.00 – 1.27	0.54 – 0.86	0.029
9	0.67 ± 0.44	0.76	0.08 – 1.27	0.47 – 0.87	0.692
10	0.71 ± 0.35	0.68	0.08 – 1.27	0.55 – 0.87	0.621
11	0.50 ± 0.40	0.42	0.00 – 1.10	0.32 – 0.69	0.022
12	0.42 ± 0.35	0.34	0.00 – 1.52	0.26 – 0.58	0.187
∑	**10.81 ± 2.65**	**11.07**	**4.72 - 14.72**	-	-

* Comparison to the previous extracted dose.

The mean trough levels found in plasma after use of the inhaler and smoking cigarettes are given in the figure 2.

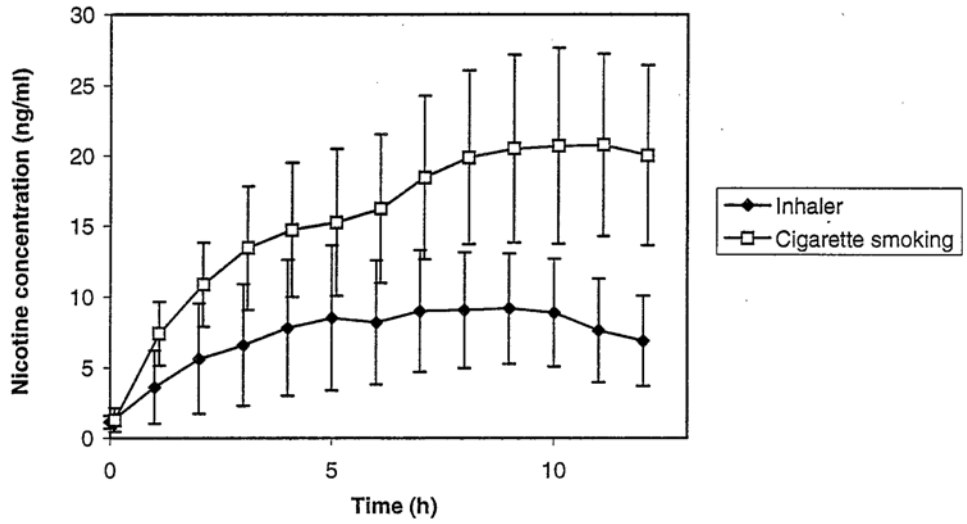

Figure 2. Mean ± SD nicotine plasma concentration versus time graph after hourly cigarette smoking and usage of nicotine inhaler, when used 8 times longer than when smoking a cigarette.

The results showed that the amount inhaled decreased slowly over time with a large inter individual variation. This is also reflected in the plasma levels of nicotine in the subjects. With cigarette smoking plateau levels are reached within 10 hours and after use of the inhaler the plateau is reach already after 5 hours. The nicotine plasma level after use of the inhaler is significantly lower compared to cigarette smoking even when the use of the inhaler takes up to 8 times longer than smoking a cigarette.

Craving and satisfaction

Before each administration the subjects rated their craving for a cigarette and the scores were measured on a 100 mm VAS. The craving was high before the first administration of both treatments. After each administration the subjects were asked if they were satisfied with the effect of the previous treatment. The scores after each treatment are listed in the table below.

Table 3. Mean ± SD and 95% confidence interval of craving and satisfaction as measured on a 100 mm VAS after hourly cigarette smoking and usage of nicotine inhaler, when used 8 times longer than when smoking a cigarette (n=21).

Adm. No.	Craving				Satisfaction			
	Nicotine inhaler		Cigarette smoking		Nicotine inhaler		Cigarette smoking	
	Mean±SD	95%CI	Mean±SD	95%CI	Mean±SD	95%CI	Mean±SD	95%CI
1	72 ± 25	60-83	70 ± 27	58-82	66 ± 21	56-75	78 ± 18*	70-86
2	40 ± 23	29-50	48 ± 17	40-55	61 ± 18	52-69	76 ± 17*	68-83
3	42 ± 29	29-55	59 ± 22*	49-70	68 ± 18	60-76	76 ± 14	70-83
4	33 ± 21	23-43	43 ± 25	32-54	72 + 15	65-79	70 ± 15	63-77
5	33 ± 23	22-43	41 ± 21	31-50	66 ± 20	57-74	57 ± 24	46-68
6	55 ± 26	43-67	65 ± 17	57-73	66 ± 18	58-74	71 ± 19	63-80
7	41 ± 26	29-53	41 ± 20	32-50	60 ± 21	50-69	69 ± 19	60-78
8	44 ± 24	33-55	41 ± 22	31-51	58 ± 22	48-69	74 ± 25*	62-85
9	46 ± 23	36-56	40 ± 26	29-52	56 ± 25	44-67	69 ± 23	58-79
10	50 ± 24	40-61	39 ± 22	29-49	45 ± 26	33-56	66 ± 27*	54-79
11	61 ± 25	49-72	53 ± 27	41-66	41 ± 30	27-54	74 ± 22*	64-85
12	58 ± 30*	44-71	32 ± 25	21-44	37 ± 33	22-52	76 ± 23*	66-86

* Significantly higher satisfaction/craving

When asked whether they would use the inhaler in the future to reduce carvings if marketed, 10 subjects declared they would, 8 would not, and 3 subjects were indecisive.

This study showed that smoking provided more satisfaction and in the end of the day reduced craving to a larger extent than the inhaler. This is to be expected, considering the lower plasma levels of nicotine obtained by using the inhaler, and considering that these are dependent patients. As no placebo was included, and the study was not blinded, no firm conclusions could be drawn.

Adverse events

A total of 38 adverse events were reported by 15 subjects after using the inhaler. No adverse events were reported after cigarette smoking. The main events included local irritation in mouth and throat and cough. Most symptoms occurred within 10 minutes and all symptoms on average within less than 20 minutes after administration. Most events were mild. There were no serious or unexpected adverse events, drop-outs of withdrawals.

Conclusion

This study showed that the nicotine exposure after rather prolonged use of the 15 mg inhaler (8 times longer than the time needed for smoking a cigarette) is only 30% in comparison with cigarette smoking. Steady sate is also reached earlier with the inhaler, probably caused by the decrease of nicotine release over time.

The fact that no adverse events were reported for smoking should be seen in the light that the subjects were smokers. Local irritability was reported for the 15 mg inhaler, probably because the nicotine and excipients are to a large extent administered on the mucosa of the throat and buccal cavity, as was reported in the dossier of the 10 mg inhaler.

Bioequivalence study I

Design

The study was conducted as a two-way cross-over, multiple-dose study in healthy smoking volunteers. The volunteers smoked at least 10 cigarettes per day. The cartridge of the new Nicorette Inhaler with 15 mg nicotine was replaced every second hour and the reference inhaler (10 mg) was replaced every hour.

The subjects did not smoke from 8 p.m. before the first treatment and were not allowed to eat anything 10 minutes before each treatment until 10 minutes after each treatment.

Inhalations were done every hour (11 hours, 12 treatments) during 20 minutes. Every subject was allowed to choose his method of inhalation: pulmonary or buccal but he of she should use the same method during the whole study.
Blood samples were taken before the first dose and after 1, 2, 4, 6, 8, 9, 10, 11, 11.17, 11.33, 11.5, 11.67, 11.83 and 12 hours after the first dose. The washout period between the periods was at least 24 hours.

The study design is considered adequate to establish bioequivalence between the two types of treatments.

Nicotine was determined in plasma with a GLC method with a nitrogen sensitive detector. The lower limit of quantitation was 0.5 ng/ml. The analytical method is considered appropriate to determine nicotine accurately and precisely. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
In total 21 subjects were recruited but only 19 subjects (8 males and 11 females; ages 22 – 48 years, weight 44 – 87 kg) completed the study. Two subjects did not comply with the standard clinical laboratory tests.
From these 19 subjects only 2 subjects used the pulmonary method of inhalation.

Table 1. Pharmacokinetic variables after repeated inhalation of nicotine by the test and reference inhaler (n=19) mean ± SD, t_{max}: median and range).

Treatment N=19	**AUC_{11-12h}** ng/ml/h	**C_{max}** ng/ml	**C_{min}** ng/ml	**PTF (%)**	**t_{max}** h
Test	19.5 ± 8.7	21.0 ± 9.3	17.8 ± 8.0	16.7 ± 4.8	11.3 (11.0 – 11.5)
Reference	18.6 ± 6.7	19.8 ± 7.0	17.0 ± 6.3	15.7 ± 6.2	11.3 (11.0 – 11.7)
***Ratio (90% CI)**	0.99 (0.88 – 1.11)	0.98 (0.88 – 1.09)	--	--	--

AUC_{11-12} area under the plasma concentration-time curve from time 11-12h
C_{max} maximum plasma concentration
C_{min} minimum plasma concentration
PTF% fluctuation index
t_{max} time for maximum concentration

**ln-transformed values*

The pharmacokinetic variables in steady state after administration of nicotine with the 10 mg inhaler replaced every hour and the 15 mg inhaler replaced every second hour is comparable. The trough values and the AUC and C_{max} after the last dose are similar and bioequivalence could be established, as the 90% confidence intervals are within the bioequivalence acceptance range of 0.80-1.25.

Bioequivalence study II
Design
The study was conducted as a two-way cross-over, multiple-dose study in healthy smoking volunteers. The volunteers smoked at least 10 cigarettes per day. With the new Nicorette Inhaler containing 15 mg nicotine the cartridge was replaced every fourth hour and the reference inhaler (10 mg) was replaced every second hour.
The subjects did not smoke from 8 p.m. before the first treatment and were not allowed to eat anything 10 minutes before each treatment until 10 minutes after each treatment.
Inhalations were done every hour (11 hours, 12 treatments) during 20 minutes. Every subject was allowed to choose his method of inhalation: pulmonary or buccal but he or she should use the same method during the whole study.

Blood samples were taken before the first dose and after 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 11.17, 11.33, 11.5, 11.67, 11.83 and 12 hours after the first dose. The washout period between the periods was at least 36 hours.
The study design is considered adequate to establish bioequivalence between the two types of treatments.
Nicotine was determined in plasma with a GLC method with a nitrogen sensitive detector. The lower limit of quantitation was 0.5 ng/ml. The analytical method is considered appropriate to determine nicotine accurately and precisely. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
In total 22 smoking subjects were recruited, of whom 21 subjects (10 males and 11 females; aged 25 – 48 years, weight 78-101 kg) completed the study. From these 21 subjects only 5 subjects used the buccal method of inhalation.

Table 2. Pharmacokinetic variables after repeated inhalation of nicotine by the test and reference inhaler (n=19) mean ± SD, t_{max}: median and range).

Treatment N=21	**AUC_{11-12h}** ng/ml/h	**C_{max}** ng/ml	**C_{min}** ng/ml	**PTF (%)**	**t_{max}** h
Test	19.21 ± 5.2	20.3 ± 5.8	17.7 ± 4.6	13.0 ± 4.6	11.3 (11.0 – 12.0)
Reference	19.2 ± 6.3	20.6 ± 6.9	17.7 ± 5.8	15.3 ± 7.6	11.5 (11.0 – 11.7)
***Ratio (90% CI)**	1.02 (0.90 – 1.10)	1.00 (0.92 – 1.08)	--	--	--

AUC_{11-12} area under the plasma concentration-time curve from time 11-12h
C_{max} maximum plasma concentration
C_{min} minimum plasma concentration
PTF% fluctuation index
t_{max} time for maximum concentration

**ln-transformed values*

The pharmacokinetic variables in steady state after administration of nicotine with the 10 mg inhaler every hour and the 15 mg inhaler every second hour is comparable. The trough values and the AUC and C_{max} after the last dose are similar and bioequivalence could be established, as the 90% confidence intervals are within the bioequivalence acceptance range of 0.80-1.25.

Conclusion of the 3 pharmacokinetic studies
When in the first kinetic study the 15 mg inhaler was compared with “normal” cigarette smoking, the trough nicotine plasma levels were only 30% after use of the inhaler.

When the new 15 mg inhaler is replaced every two or four hours in the two bioequivalence studies respectively, the exposure to nicotine is comparable with the use of the 10 mg inhaler if the cartridge is replaced every hour of every second hours, respectively.

The bioequivalence studies support the results of *in-vitro* studies, indicating that increasing the amount of nicotine in the cartridges from 10 to 15 mg does not influence the inhaled nicotine dose, as the air is saturated with nicotine as long as the remaining nicotine content in the cartridge is above 3 mg. This ceiling effect for the saturation is confirmed by the pharmacokinetic data, as C_{max} was equivalent for fresh 10 and 15 mg cartridges.

If patients would refill the inhaler-device with a 15 mg cartridge as frequently as they would normally do with the 10 mg cartridges, no significant accumulation is expected. The only difference is that cartridges

will have to be refreshed sooner for the 10 mg than for the 15 mg cartridge. At some point after multiple inhalations, the cartridge will not contain sufficient nicotine anymore to saturate the air-flow (3 mg is the minimal amount of nicotine needed in the cartridge), and this time point will be achieved earlier for the 10 mg than for the 15 mg cartridge. The patient will notice this, and refresh the cartridge at individual need, as recommended in the SmPC. As plasma exposure will be largely similar between 10-15 mg inhaler at auto-titration, efficacy can be extrapolated from the 10 mg dossier.

Smoking was significantly more satisfactory to reduce craving than the device. This is to be expected, as plasma levels after using the device are lower than after smoking. But since no placebo was included, no firm conclusions could be drawn about reduction of craving.

Local tolerability was less favorable after using the 15 mg device compared to smoking (5 subjects had mild-moderate adverse events versus none for smoking).

There is a large safety margin, as the nicotine plasma levels after using the 15 mg cartridge for 20 minutes, were 3 to 4 times lower than the levels achieved by cigarette smoking. From a safety point of view, the 15 mg dose is therefore considered acceptable.

The less frequent need for refreshing the cartridges is considered beneficial for the consumer and the environment. As there is no increased risk of systemic adverse events at a 15 mg dose, because C_{max} is similar, the benefit/risk profile is considered positive.

Risk management plan

The MEB considers that the Pharmacovigilance system as described by the MAH fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The MAH submitted a Risk Management Plan for Nicotine 15 mg Inhaler, developed to support the application request for the marketing of nicotine 15 mg inhaler in the European Union (EU) for the treatment of tobacco dependence.

Product information

SmPC

The content of the SPC approved during the national procedure is in accordance with that accepted for other Nicorette Inhaler 10 mg.

Readability test

The package leaflet has not been evaluated via a user consultation study. Instead, a bridging report has been provided. Reference is made to successful readability testing that was performed on the Belgian (Flemish) version of the Nicorette Inhaler 15 mg package leaflet. The Dutch and Belgian versions of the package leaflet differ only in small textual parts.
Because of the fact that the contents of the Dutch and the Belgian language versions are nearly identical and therefore the critical efficacy and safety key messages of both leaflets are identical, the results of the readability test of the Belgian are also valid for the Dutch version. Separate user testing is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Nicorette Inhaler 15 mg, inhalation vapour, liquid has a proven chemical-pharmaceutical quality and is an approvable line extensions to Nicorette Inhaler 10 mg. Nicorette Inhaler is a well-known medicinal product with an established favourable efficacy and safety profile.

When the 15 mg inhaler was compared with “normal” cigarette smoking, the trough nicotine plasma levels were shown to be only 30% after use of the inhaler. Bioequivalence between the 10 mg inhaler and the new 15 mg inhaler has been shown to be in compliance with the requirements of European guidance documents. The refreshing of cartridges is less frequent with the 15 mg inhaler, which is considered beneficial for the consumer and the environment. As there is no increased risk of systemic adverse events at a 15 mg dose, the product is considered approvable.

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

The SmPC is consistent with that of the 10 mg inhaler. The SmPC, 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 Inhaler 15 mg, inhalation vapour, liquid was authorized in the Netherlands on 11 December 2012.

There were no post-approval commitments made during the procedure.

List of abbreviations

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
SmPC	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
Submission of a new colour package mock-up.	--	61(3)	9-7-2013	9-8-2013	Approval	N