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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Nicorette Inhaler 10 mg, inhalation vapour, liquid

Marketing authorisation holder:
at the time of registration: Pharmacia & Upjohn B.V., the Netherlands
since 9 July 2009: 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 and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states 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 18113

8 May 2012

Pharmacotherapeutic group:	drugs used in nicotine dependence
ATC code:	N07BA01
Route of administration:	inhalation use
Therapeutic indication:	Relieving or treating severe nicotine withdrawal symptoms upon quitting smoking
Prescription status:	prescription only
Date of first authorisation in NL:	25 July 1996
Application type/legal basis:	national application, equivalent to Article 3.7 "Regeling Geneesmiddelenwet" (Article 8.3, Directive 2001/83/EC)

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 Inhaler 10 mg, inhalation vapour, liquid, from Pharmacia & Upjohn B.V. (transfer of the marketing authorisation to Johnson & Johnson Consumer B.V. approved on 30-07-2009). The date of authorisation was on 25 July 1996 in the Netherlands.

The product is indicated for relieving or treating severe nicotine withdrawal symptoms upon quitting smoking.

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

Various forms of nicotine replacement therapy have been used to help people quit smoking. Abruptly stopping with the use of products that contain tobacco after a prolonged period of daily use results in a characteristic withdrawal syndrome, including four or more of the following symptoms: depressive symptoms, insomnia, irritability, frustration or anger, anxiety, concentration problems, restlessness or impatience, reduced heart rate and increased appetite or weight gain. Clinical studies have shown that nicotine replacement products can help smokers quit smoking by relieving these withdrawal symptoms.

Following the chewing gum, the transdermal patches and the nasal spray, the Nicorette inhaler is another formulation to administer nicotine to reduce the symptoms of the tobacco withdrawal syndrome. The recommended dosage is as needed between 6 and 12 inhalation cartridges per day, thereby offering patients the potential to self titrate their dose

During continuous forced inhalation, the largest fraction of the nicotine dose attaches to the buccal mucosa in the oral cavity. Absorption of nicotine through the buccal mucosa is relatively slow and does not provide fast or high nicotine plasma levels comparable to cigarette smoking. The nicotine plasma levels of Nicorette Inhaler when used as needed, are about 1/3 of the levels when smoking a cigarette. The plasma levels after recommended use of Nicorette Inhaler correspond to those of Nicorette 2 mg gum (1 gum per hour) and Nicorette Nasal Spray (1 dose per hour).

The therapeutic concentration of nicotine in the blood or the nicotine plasma levels that reduce the need to smoke, are individual and are determined by the nicotine dependence.

This national procedure concerns a line extension to the existing marketing authorisation of Nicorette 2 mg kauwgom, medicated chewing-gum (NL License RVG 09155) by Johnson & Johnson Consumer B.V., which has been registered in the Netherlands since 17 March 1983 (original product). With this application the new dosage form of liquid inhalation vapour is introduced.

This procedure concerns a national application, equivalent to Article 3.7 of the “Regeling Geneesmiddelenwet” (Article 8.3, Directive 2001/83/EC). It concerns a so-called full dossier application, a dossier with administrative, chemical-pharmaceutical, pre-clinical and clinical data. The active component, nicotine, is considered to be well-known and the clinical pharmacology of nicotine has been extensively studied. The MAH submitted a number of toxicological, pharmacokinetic, pharmacodynamic and clinical studies to support the line extension.

The MAH had not consulted the MEB for Scientific Advice before application. No paediatric development programme has been submitted, as this was not a requirement at the time of registration.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (applicable at the time of registration) are in place for these product types 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 to pale yellow liquid. It is volatile, hygroscopic, alkaline, soluble in water and miscible with ethanol. It tends to discolour upon unprotected storage due to its susceptibility to oxidation.

Manufacturing process
Details concerning the manufacturing process of the active substance were available to the MEB in closed part of the DMF. The manufacturing steps have been assessed.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the Drug Master File (DMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and 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, light protected and under argon in an airtight sealed container consisting of rolling chanel drums made of cold rolled sheet metal. Assessment of stability studies was part of assessment of the DMF.

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

Medicinal Product

Composition
Nicorette Inhaler 10 mg consists of a porous plug of polyethylene, serving as a reservoir for nicotine. The porous plug, loaded with 10 mg nicotine, is inserted in a sealed, transparent, plastic tube. 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 Nicorette Inhaler 10 mg has a maximum of 3.5 mg when 10 liters of air has passed through the nicotine loaded porous plug. However, the delivery of nicotine is dependent on the temperature of the air stream.
The pharmaceutical dosage form is inhalation vapor, liquid. Excipients are levomenthol, nitrogen and a porous polyethylene plug. Levomenthol is used as a flavouring agent. The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The porous plug is a high density polyethylene plug, which is the carrier material for nicotine and the flavouring agent levomenthol. The mouthpiece is sufficiently tested concerning the resistance to the air flow drawn through the cartridge and the possible loss of nicotine. The pharmaceutical development of the product has been adequately performed in accordance with the relevant European guidelines.

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.

Excipients

The used excipients are well known and safe in the proposed concentrations. The excipients comply with the Ph.Eur, or in-house specifications. These specifications are acceptable.

Container closure system

The Nicotine Inhaler 10 mg container closure system consists of plastic tube, in which the nicotine loaded plug is inserted before the tube is sealed at both ends by a foil. The unit (cartridge) is placed into a mouthpiece and the seals are broken when the mouthpiece is assembled. The user then draws air through the porous plug, which releases nicotine to the air stream. The mouthpiece is made of polypropylene. The packaging materials comply with relevant guidelines.

When the cartridge is inserted in the mouthpiece, both ends of the cartridge are penetrated, allowing air to pass through it (see below).

The mouthpiece ready to use is shown below.

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 criteria are considered to be 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 and three commercial scale batches, demonstrating compliance with the release specification.

Stability of drug product

Sufficient data was submitted upon storage at 25°C, 30°C and 40°C to support the claimed storage period of 3 years when stored below 25°C. The conditions used in the stability studies are according to the guidelines appropriate at the time of registration. The batches were stored in the commercial packaging material.

II.2 Non clinical aspects

Toxicology

Inhalation toxicity study

The submitted dossier contained a few studies on nicotine inhalation. Four test models were compared against two reference cigarettes. However, the data submitted was not considered valid by the MEB for estimation of the local tolerance because the (non-GLP) study lacked a description of the methodology used, and the study was described very briefly. Submitted data from a 26-week study in hamsters could also not be used for the assessment of the local tolerance, as only an abstract was included.

One 5-day range finding inhalation study in rats was submitted, in which three groups of ten CD rats (5 male and 5 female) were exposed (head-only) to atmospheres containing nicotine hydrogen tartrate particles of varying size and concentrations, twice daily for 90 minutes for five consecutive days. The control group was exposed to room air. The achieved dose levels per day in the groups were 589, 4714 and 13072 µg/kg/day. Plasma levels of nicotine on day 1 were 14.1, 87.5 and 202 ng/ml, respectively. Corresponding cotinine levels on day 1 were 61.9, 276.3 and 514.8 ng/ml respectively. Plasma levels of nicotine on day 5 were 19.1, 108.0 and 216.9 ng/ml, respectively. Corresponding cotinine levels on day 5 were 79.4, 341.5 and 754.3 ng/ml respectively. Both nicotine and cotinine were found at low concentrations (2-7 ng/ml) in control animals. Both nicotine and cotinine accumulated during the study.

No deaths or treatment related clinical signs were observed during the study. A significant decrease in body weight attributed to reduced food consumption was found in high dose males. No histopathological changes were seen in the respiratory organs like trachea and lung (control and high dose examined only).

Discussion on toxicology

Although the study in rats covered a 26-week period, no final study results were submitted. During the registration procedure it was discussed whether the 5-day range-finding study in rats is sufficient to prove the absence of local toxicity (in the respiratory tracts) in long term treatment. Complete study results from the 26-week toxicity study were not available to the MAH. The MAH considered data from the 5-day study in rats, combined with published data sufficient. From cigarette smokers it is not known whether nicotine has major irritating effects on the respiratory tract. This finding can be extrapolated to Nicorette Inhaler. From an animal welfare point of view, it is not considered appropriate to ask for further animal studies on local tolerance. Therefore, although the local tolerance cannot be assessed from animal studies, it was concluded that the absence of local tolerance problems with traditional cigarette smokers can be extrapolated to Nicorette Inhaler.

II.3 Clinical aspects

Pharmacokinetics

The MAH submitted a number of human pharmacokinetic studies. One study focused on the dose and absolute bioavailability of nicotine from the nicotine inhaler when used in two standardized ways, i.e. by deep inhalation (pulmonary)) and frequent suckling shallow inhalation (buccal). Fourteen volunteers participated in a three-way cross-over study. Based on the area under the plasma concentration vs. time curve, the absolute bioavailability was 57 ± 16% (pulmonary mode) and 54 ± 19% (buccal mode), respectively. It was concluded that different inhalation pattern resulted in similar absorption of nicotine.

Another study focused on the amount of nicotine available to the systemic circulation from the Nicorette Inhaler 10 mg. This study was an open cross-over comparison with an intravenous infusion in a sub-set of as many subjects as possible participating in this study. Twelve subjects were eligible for analysis. According to the authors of the report, the aim of the study was to determine the amount of nicotine available to the systemic circulation from the inhaler. However, as the authors also conclude in the report, this study is not a good bioavailability study since the amount of nicotine released from the inhaler as indicated by a 4-5 fold variation in the amount available to the systemic circulation, seems to be caused the performance of the subject him-/herself, e.g. in terms of depth of inhalation. No conclusion on the bioavailability of nicotine from the inhaler can be drawn from this study. It only gives some indication on the performance of the inhaler and/or the subject.

Also a study was performed focusing on a comparison of nicotine plasma levels after repeated dosing with the Nicorette inhaler and 2 mg Nicorette chewing gum. Eighteen volunteers (eight males, ten females) participated in this open randomized, two-way cross over study. Multiple doses, using strictly standardized modes of administration were applied. The gum was chewed every two seconds for 20 minutes. The inhaler was used by means of deep inhalations (five seconds) every 15 seconds for 20 minutes. The study medications were used once every hour for 10 hours. Serial blood samples were drawn for determination of trough nicotine levels as well as nicotine levels during the last dosing interval.
The total dosage was one inhaler each hour, in total eleven inhalers; one gum each hour, with a total of 11 gums containing 2 mg nicotine each. The following pharmacokinetic parameters were determined: C_{max}, T_{max}, C_{trough} and AUC_{10-11} (area under the plasma concentration time curve during the last dosing interval).
The results from this study showed that the mean trough plasma nicotine levels (i.e. the plasma levels at the end of dosing period, just before the new dose) were approximately 2.5 times as high after the use of the inhaler as after chewing gum at all time points. The values at 9, 10, and 11 hours were 22.8 ± 8.2, 22.5 ± 7.5 and 22.4 ± 8.5 ng/ml, and 8.4 ± 1.6, 8.7 ± 1.5 and 9.3 ± 1.7 ng/ml after the inhaler and the gum, respectively. Large differences are noted in inter-individual variability, which is much higher for the inhaler than for the gum.
Interestingly, nicotine release was found dependent on environmental temperature, and the dose available to the systemic circulation is increased by approximately 35% for every 10°C increase of environmental temperature. However, it was concluded that Nicorette Inhaler would not produce nicotine plasma levels exceeding those achieved when smoking cigarettes not even after one day's maximal puffing in a hot climate.

Discussion on pharmacokinetics
It was noted that steady state plasma levels are not comparable to plasma levels after Nicorette gum, but more variable and about 2.5 times higher. Questions were raised regarding the large inter-individual (between subjects) variability in plasma levels. Consequently, the exact applied doses are difficult to forecast for individual patients.
In response, the company submitted data from a new pharmacokinetic study with Positron Emission Tomography (PET), concerning nicotine deposition and body distribution from a nicotine inhaler and a cigarette. The site of deposition of nicotine was studied with PET (^{11}C-nicotine), after a nicotine inhaler (one deep inhalation for 5 seconds every 15 seconds, for 5 minutes) or smoking a cigarette in an open two-way cross-over design. The pharmacokinetic study with PET showed that a significant amount of nicotine from the inhaler is swallowed and transferred to the stomach after deposition in the oral cavity. A minimum fraction of the dose is recovered in the lungs. In addition, the nicotine plasma levels of Nicorette Inhaler when used as needed, are about 1/3 of the levels when smoking a cigarette.

Based on these data showing a lower exposure of the inhaler compared to smoking cigarettes, the MEB considered the point of the high variability not as a safety issue, but more a point of reliability of the study. Based on the pharmacokinetic profile and variability, the MAH accepts this product as being more like the Nicorette Nasal Spray application, than similar to the gum (Nicorette Nasal Spray NL license RVG 16964, voluntary withdrawn on 31 December 2005, not because of a safety issue).

Pharmacodynamics
Nicotine has a wide variety of stimulant and depressant effects that involve the central and peripheral nervous, cardiovascular, endocrine, gastrointestinal and skeletal motor systems. Two issues are particularly relevant to the pharmacodynamics of nicotine: a complex dose-response relationship and the development of tolerance by exposure to nicotine. At doses as seen during cigarette smoking, cardiovascular effects predominate, with an increase in blood pressure and heart rate. Initial exposure to cigarette smoking commonly produces dizziness, nausea and vomiting, effects to which the smoker rapidly becomes tolerant.

In response to a request of the MEB during the procedure, the MAH provided literature on dependence potential or the abuse liability of the Nicotine Inhaler. One study included an early prototype for nicotine vapor inhalation and found the prototype to produce plasma levels of about 1/3 of levels achieved by cigarette smoking. In a placebo-controlled, four-way cross-over study on the effect of ad libitum use of the Nicorette Inhaler on craving and other withdrawal symptoms during a two-day smoke-free period, active treatment significantly decreased the craving and withdrawal symptom scores.

In the literature review it is stated that the nicotine chewing gum and patches are effective only in suppressing abstinence but do not influence the behavioral reinforcement items, such as euphoria etc. This issue was already sufficiently discussed for the Nicotine Nasal Spray application (NL license RVG 16964, voluntary withdrawn on 31 December 2005) in relation to the potential higher risk of abuse due to the fast absorption (now clearly indicated by the company as a risk factor). The MAH indicated that the inhaler differs from the other nicotine systems in that the "puffing" allows continuing reinforcement of some sensory, oral and handling behavior. It was clearly stated that the risk on a higher abuse liability because of a more rapid increase in the plasma concentration of nicotine, was well known at beforehand. The goal of these formulations (Nasal Spray and Inhaler) explicitly was to give more 'liking' to the users than the gum and patches. Especially for the more serious cases of dependence these new forms should be more effective. Therefore, the restrictions indicated for the Nasal Spray are also applicable to the Inhaler.

Clinical studies

Study design
Six pivotal double-blind, randomized, placebo-controlled studies in smoking cessation have been carried out (study reference numbers 44-49). Treatment consisted in all studies of ad libitum usage of inhalers with a maximum of 10 inhalers per day in three studies (44-46) and 20 inhalers per day in two (48,49), and no limit in one (47). Recommended minimum dose was use of at least 2 inhalers per day in three studies (44-46). Due to divergent results in these three studies, a minimum use of at least 4 inhalers per day was recommended in the next three studies (47-49). The dosage regimen was to be continued up to the three months visit and thereafter, if considered necessary, a tapering period of maximum another 3 months. No further medication was dispensed after the six months visit. The tapering period was carried out by dispensing for month 4: 75%, month 5: 50% and month 6: 25% of the number of inhalers used at 3 months. The objectives of the studies were, first, to determine if there is a difference in smoking cessation success between Nicorette Inhaler and placebo, and second, to investigate possible adverse events of Nicorette Inhaler compared to placebo.
Based on previous experience with smoking cessation studies, it was assumed that the placebo would produce a success rate of 20%, and active treatment a success rate of 40% at 12 weeks (3 months). Thus, it was calculated that the two groups had to comprise 110 subjects each to achieve a significance level of 5% with a power of 90%. All six pivotal studies succeeded in including sufficient patients

Clinical efficacy
Criteria for efficacy can be based on three different definitions of success:

- Completely abstinent from week 2 of treatment.
- Completely abstinent for all sessions.
- Abstinence for all sessions from week 2, slips allowed

Assessment of abstinence was based on self-report, combined with a carbon monoxide level in exhaled air below 10 ppm at sessions to provide objective testing. Subjects who were smoking at week 3 or later, or who did not return to the clinic in spite of two reminders were regarded as failures and withdrawn from the study. Table A summarizes the results of these six trials.

The first three studies (44-46) showed divergent results in efficacy, one study showing no difference in success rate between active compound and placebo (46), another showing significant difference (44), and the last study with a result in between (45). The most plausible explanation issues compliance to the prescribed therapy. The compliance was high in study 44 with only 13% on active and 16% on placebo using less than two inhalers per day (the recommended minimum dose) in the beginning of treatment. Study 46 did not show active treatment being superior to placebo at any time-point, although extensive individual intervention was used. Compliance in this study was however poor, with 54% on active and 52% on placebo using less than two inhalers per day. The outcome due to the low use of active inhalers may present a placebo effect also in the active treatment group rather than a pharmacological effect. When efficacy is assessed as abstinent all sessions from week 2, slips allowed, significant differences are found between active and placebo treated patients.
The MAH argued that analyses of the first three studies indicated that, to achieve success, the following criteria should be considered:

- At least 4 inhalers should be used initially for the first 3 to 6 weeks based upon retrospective cotinine (i.e. nicotine metabolite) analysis, showing that at least a degree of substitution of 20% (geometric mean) should be obtained to enhance success. This corresponds to experiences with the nicotine chewing gum, nicotine patches and Nicorette Nasal Spray,
- probably only a minimum of supportive intervention is needed (perception at the time of registration), and
- the concept of how to use the inhaler is very important.

Based on these considerations the next three studies were conducted (47-49). Analyses of these studies confirm the value of adequate dosing in the beginning of treatment with an average use of not less than 6 inhalers per day.

Discussion on clinical studies

The key issue is whether there is a significant difference in success rate between placebo and actively treated patients 6 months after stopping study medication. At the time of first assessment, of the six pivotal studies only three provided sufficient follow-up data and only one showed such a difference. It was argued that the initial dose used in the other two of these studies was too low. Therefore, in the three following studies submitted in a later phase the use of at least 4 inhalers daily for the first 3 to 6 weeks was a requirement. After initial assessment it was concluded that Nicorette Inhaler could only be considered for registration when the results of the long term follow-up of the latter studies showed a satisfactory difference in smoking cessation rate.

In the response phase the company submitted reports concerning the long-term follow-up for the clinical studies with results presented of the 12 months follow-up (6 months after stopping study medication). These results are presented in table A. This report provides clearly tabulated summary data and calculated odds ratios (OR). In addition to one of the three earlier studies, also one of the three pivotal studies showed a statistically significant difference in abstinence rate at 12 months in favor of active treatment (this result was similar for either long-term efficacy defined as complete abstinence from week 2, or from quit day).

Table A: abstinence in all Nicorette® inhaler studies, % of patients, active treatment vs placebo. The additional data from the studies employing adequate dose [47,48,49] are presented in the lower half of the table. OR = Odds Ratio

	abstinence from week 2 (quit day) through all visits no slips allowed								abstinence from week 2 through all visits slips allowed							
outcome	6 months %				12 months %				6 months %				12 months %			
study	act	pla	p	OR	act	pla	p	OR	act	pla	p	OR	act	pla	p	OR
Tonnesen [44] n=144+140	19	10	0.036	2.077	17 (15)	6 (5)	0.004	3.300	25	11	0.002	2.778	19	6	0.002	3.359
Glover [45] n=129+112	17	15	NS	1.149	13 (11)	14 (13)	NS	0.911	30	18	0.026	1.993	22	18	NS	1.275
Sachs [46] n=112+111	14	20	NS	0.674	12 (11)	18 (17)	NS	0.597	21	24	NS	0.804	15	20	NS	0.724
Hjalmarson [47] n=123+124	35	19	0.004	2.360	29 (28)	18 (16)	0.033	1.918	37	21	0.007	2.175	32	19	0.017	2.039
Leischow [48] n=111+111	21	6	0.022	3.883	11 (8)	5 (5)	NS	2.121	28	8	<0.0005	4.392	15	7	NS	2.328
Schneider [49] n=112+111	22	11	0.021	2.371	13 (13)	10 (10)	NS	1.406	34	13	<0.0005	3.558	20	12	NS	1.843
All 6 studies n=1440 (95% CI)				1.776* (1.340-2.353)				1.452** (1.070-1.972)				2.215* (1.709-2.871)				1.679* (1.265-2.228)

*: p <0.001 **: p <0.002

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The analysis at 12 months of the three clinical studies that used adequate inhaler doses, showed higher abstinence rates for actively treated patients compared to placebo but the difference reached statistical significance at the 5% level in only one. Due to the low abstinence rate, the numbers of patients in studies 48 and 49 were probably too small to detect a real difference. Statistically significant efficacy was shown when all six studies were taken together, with an OR of 1.45. Thus the overall analysis supports the long-term efficacy of Nicorette Inhaler therapy.

Clinical safety

No serious systemic adverse events were found. Most frequent spontaneous reported complaints were headache (21% in the active group and 17% in the placebo group), heartburn (5% and 1%, respectively), and nausea (7% and 5%, respectively). Angina pectoris was not reported with active therapy in any of the six pivotal trials.

Local irritant adverse events occurred most often in the early stages of treatment. The most frequent complaints were cough, and irritation in mouth and throat. Overall, these complaints were rated as mild. On specific questioning during the first week of treatment, cough was reported in 44% of the active group and 26% in the placebo group. For irritation in mouth/throat these figures were 44% and 23%. At the third week of treatment these percentages had decreased to 29% and 20%, and 31% and 16%, respectively. To open-ended questions, the percentage of patients reporting about side effects was considerably lower.

Due to adverse events, 12 subjects on active treatment (1.6%) and 15 subjects on placebo treatment (2.0%) were withdrawn from the studies. A comprised tabulation over systemic and local adverse events with an incidence of more than one percent is presented in table B (adverse events in all 6 studies and recalculated for the total follow-up to 12 months). No reports of over dosage have occurred during the clinical studies. The Inhaler is not likely to cause overdose symptoms, as maximum plasma nicotine levels produced are about 1/3 of the levels found when smoking.

Table B: pooled adverse events in studies 44 - 49

Pooled Adverse Event Report up to 1 Year, Including 6 Months Follow-up

This table comprises pooled adverse events from six studies: Tønnesen (44), Glover (45), Sachs (46), Hjalmarson (47), Leischow (48) and Schneider (49)

	Active Inhaler N=731		Placebo Inhaler N=709		Incidence Active > Placebo + 1%
ADVERSE EVENTS	Total	%	Total	%	
Systemic Effects					
Headache	156	21.3	123	17.3	4.0
Heartburn	39	5.3	10	1.4	3.9
Hiccup	11	1.5	0	0.0	1.5
Nausea	50	6.8	37	5.2	1.6
Pain	27	3.7	20	2.8	1.0
Vomiting	12	1.6	2	0.3	1.4
Flatulence	13	1.8	5	0.7	1.1
Local Effects					
Burning/Smarting Localized	17	2.3	0	0.0	2.3
Burning/Smarting Mouth	11	1.5	2	0.3	1.2
Canker Sores Oral	15	2.1	6	0.8	1.3
Coughing	159	21.8	53	7.5	14.3
Mouth Irritation	40	5.5	13	1.8	3.6
Nose Congestion	34	4.7	24	3.4	1.3
Sinusitis	23	3.0	11	1.6	1.5
Throat Irritation	100	13.7	28	3.9	9.7
Throat Sore	76	10.4	39	5.5	4.9

Proposed dosing scheme

Another point in the discussion during the registration procedure was that the SPC advised a different dosing scheme than described in the protocol used in the pivotal clinical trials. The SPC advised to use the inhaler during 2 months, with subsequently 1 month dose tapering. The minimum dose to be used in first 8 weeks is stated to be 6 inhalers per day. The MAH analyzed the average daily use of active inhaler in the last three studies, which resulted in slightly higher success rates (47-49). The relevant data of his analysis are summarized in table C. Maximal treatment duration is 6 months.

Table C: average daily use of active inhaler in studies 47-49 during the first 6 weeks of the treatment period in relation to abstinence

	week 1-3 n=346		week 1-6 n=346	
abstinent at	mean	95% CI	mean	95% CI
completely abstinent				
6 months	6.1	3.7 - 8.5	5.9	3.3 - 8.6
12 months	5.9	3.6 - 8.1	5.7	3.0 - 8.3
sustained abstinence, slips allowed				
6 months	6.0	3.5 - 8.5	5.8	3.2 - 8.4
12 months	5.9	3.2 - 8.6	5.7	2.8 - 8.6

The MEB decided to include in the SPC a dosing schedule comparable to the dosing scheme used in the clinical studies.

Comparison with currently registered nicotine-containing products
The MEB concluded that comparative studies between Nicorette Inhaler and currently registered nicotine-containing products are needed for a clear insight in the position of Nicorette Inhaler among the other products.
In the response phase the MAH presented a comparison of two consecutive studies performed on nicotine patches of 15 mg and Nicorette Inhaler (2-10/day) respectively (study 44, described above). The number of patients were 289 and 284 respectively and the in- and exclusion criteria were similar. Compliance was similar. Results are shown in table D.

Table D: Complete abstinence from quit day, patch vs inhaler

	patch				inhaler					
	active		placebo		active		placebo			
Time	%	N	%	N	%	N	%	N	p1	p2
6 weeks	30	43	4	6	28	40	12	17	ns	0.014
3 months	26	37	3	4	21	30	9	13	ns	0.021
6 months	17	25	2	3	17	25	8	11	ns	0.025
12 months	11	16	2	3	15	22	5	7	ns	0.213

p1= p-value difference active treatment p2 = p-value difference placebo treatment

The primary outcome parameter was complete abstinence from quit day. There were no differences in the response to active treatment of the patch and inhaler, but the placebo response was higher for the inhaler study. The MAH argued that the initial higher success rate in the placebo group is possibly due to a behavioral compensation from inhaler device. In both studies significant better outcome was found for patients on active treatment versus placebo at 6 weeks till 6 months.
The presented data suggest an equal outcome for patch and inhaler nicotine-replacement therapy.

Dependence potential
The MEB assessed the risk of abuse and dependence. Abuse liability has been mentioned for the first time with nicotine replacement therapy with Nicorette Nasal Spray. Pharmacokinetic properties that

presumably contribute to persistent self-administration and abuse include, among others, rapid absorption and delivery of the drug to the central nervous system. Nicotine from tobacco smoke for instance, is rapidly absorbed and transferred into the brain. This results in high brain concentrations and psychological effects, with relatively little development of tolerance. The smoker may titrate the level of drug and associated psychological effects of nicotine. Thus, smoking provides a nearly optimal situation for behavioral reinforcement. A similar pharmacokinetic profile has been found with Nicorette Nasal Spray. However, the present formulation (Nicorette Inhaler) has a different profile. Indirect comparison of data indicates that C_{max} with the Inhaler is considerably lower, and moreover, T_{max} is later when compared to Nicorette Nasal Spray and/or smoking. Nicorette Inhaler may therefore be expected to have less dependence potential.

In the clinical studies, a reduction over time of number of Inhalers used per day has been noticed, indeed indicating a low potential for dependency. In three studies (44-46) 38% of abstainers were using active inhalers after six months of therapy, representing 10% of the total number of subjects assigned to active inhaler treatment. Only 1% of subjects assigned to placebo was still using the placebo inhaler at that time point. Before the tapering phase at three months in the three other pivotal studies (47-49), 69% of abstainers were using active inhalers, representing 54% of the total number of subjects assigned to active inhaler treatment. None of the subjects participating in any of the studies has been allowed to use the Inhaler for a longer period than six months.

It was agreed that the dependence potential of Nicorette Inhaler is expected to be less than that of Nicorette Nasal Spray for reasons of pharmacokinetics (lower and later C_{max}), and also that the reduction over time of the number of inhalers noticed in the clinical studies indicated a low dependence potential.

Product information

SPC

The content of the SPC approved during the national procedure is in accordance with those accepted for other Nicorette products.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Nicorette Inhaler 10 mg, inhalation vapour, liquid has a proven chemical-pharmaceutical quality and is an approvable line extension to Nicorette 2 mg kauwgom, medicated chewing-gum (NL License RVG 09155). Nicorette 2 mg kauwgom, medicated chewing-gum is a well-known medicinal product with an established favourable efficacy and safety profile.

In the Board meeting of 22 June 1995, issues discussed included the data on local toxicity, large inter-individual variability in nicotine plasma levels in submitted studies, the abuse and dependence potential of the product, long-term efficacy, the proposed dosing scheme and data concerning the comparison of the Nicorette Inhaler with already registered nicotine containing products.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that quality, efficacy and safety were demonstrated. Therefore, the Board granted a marketing authorisation. Nicorette Inhaler 10 mg, inhalation vapour, liquid was authorised in the Netherlands on 25 July 1996.

The SPC, package leaflet and labelling are in the agreed templates.

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

List of abbreviations

AE	Adverse event
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
CNSRD	Chronic Non-specific Respiratory Disease
COPD	Chronic Obstructive Pulmonary Disease
C_{trough}	Trough plasma levels
CV	Coefficient of Variation
DMF	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
NRT	Nicotine Replacement Therapy
OR	Odds ratio
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
PET	Positron Emission Tomography
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
r.a.	Radioactivity
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	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Update specifications active substance according to update USP.	I	21-08-1997	25-08-1997	Approval	N
Change in qualitative composition of immediate packaging material and container shape.	I	22-08-1997	09-09-1997	Approval	N
Changes in manufacture of the medicinal product and change in batch size of the finished product.	I	04-09-1997	22-09-1997	Approval	N
Changes in test procedures of the medicinal product	I	08-09-1997	17-09-1997	Approval	N
Change name manufacturer of the medicinal product, change manufacturer active substance, minor change manufacturing process of the active substance.	I	29-10-1997	24-11-1997	Approval	N
Periodic safety update report (PSUR)		21-11-1997	15-01-1998	Approval	N
Addition manufacturer plastic tube, update specifications	I	08-01-1998	14-04-1998	Approval	N
Periodic safety update report (PSUR)		22-04-1998	31-07-1998	Approval	N
Change in specification of the medicinal product.	I	4-06-1998	17-07-1998	Approval	N
Changes in qualitative composition of immediate packaging material and change in container shape.	I	05-06-1998	17-07-1998	Approval	N
Update DMF, update specifications active substance.	Update upon request MEB	07-07-1998	06-10-1998	Approval	N
Periodic safety update report (PSUR)		09-10-1998	21-01-1999	Approval	N
Change prescription status, update PIL and labelling.	II	05-02-1999	18-10-1999	Approval	Y
Update user manual in PIL.	I	18-10-1999	09-02-2000	Approval	N
Update PIL (contra indications regarding pregnancy and lactation) and minor update labelling.	I	23-03-2000	26-05-2000	Approval	N
Change specifications medicinal product, update test method.	II	15-03-2000	30-05-2000	Approval	N
Update DMF applicant's part, inclusion Ph. Eur. monograph for nicotine.		29-05-2000	12-01-2001	Approval	N
Extension shelf life medicinal product	I	31-07-2000	15-09-2000	Approval	N
Change specification mouth piece and cartridge, addition manufacturer mouth piece.	I	02-02-2001	27-02-2001	Approval	N
Change marketing authorization holder.		02-02-2001	09-03-2001	Approval	N
Periodic safety update report (PSUR)		28-09-2001	02-09-2003	Approval	N
Change test procedures medicinal product.	I	25-01-2002	15-02-2002	Approval	N
Extension of the indication.	II	19-12-2000	04-01-2002	Partially approved	Y
Harmonization product information.	I	31-01-2002	02-07-2002	Approval	N
Change name manufacturer.	I	07-05-2002	28-06-2002	Approval	N

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change from DMF to CEP for active substance manufacturer, update specifications.	II	20-03-2002	12-09-2002	Approval	N
Change marketing authorization holder.		05-03-2004	16-03-2004	Approval	N
Change name manufacturer finished product.	I	11-03-2008	15-04-2008	Approval	N
Change marketing authorization holder.	I	16-05-2008	02-07-2008	Approval	N
Periodic safety update report (PSUR)		19-09-2008	09-03-2009	Approval	N
Update product information following PSUR.	II	15-06-2009	21-09-2010	Approval	N
Change name and address of marketing authorization holder.	I	18-06-2009	09-07-2009	Approval	N
Change primary packaging not in contact with finished product.	I	26-07-2010	13-08-2010	Approval	N
Change to an existing pharmacovigilance system as described in the DDPS.	I	22-12-2010	14-02-2011	Approval	N
Deletion active substance manufacturer, update CEP, change to comply with Ph. Eur, change test procedure active substance.	I	23-12-2010	10-02-2011	Approval	N
Change to an existing pharmacovigilance system as described in the DDPS.	I	15-04-2011	17-06-2011	Approval	N
Change in manufacturing process of the finished product.	I	19-08-2011	18-10-2011	Approval	N
Periodic safety update report (PSUR)		31-10-2011	13-02-2012	Approval	N

Annex I – Change of the prescription status from prescription only to non-prescription

I RECOMMENDATION

Based on the review of the data on safety, the MEB considers that the variation application for Nicorette Inhaler 10 mg for a change of the prescription status from prescription only to non-prescription is approvable.

Major objections have been solved and the product information has been amended accordingly.

II EXECUTIVE SUMMARY

II.1 Scope of the variation

In February 1999, the MAH submitted a Type II variation for Nicorette Inhaler 10 mg via a national procedure. The aim of the application was to switch the available nicotine inhaler from prescription only status to a non-prescription product. For this goal the company submitted a clinical expert report which summarizes the safety of nicotine inhaler. It was not necessary to demonstrate efficacy as this compound is licensed already.

II.2 Supplementary paragraph

The Nicorette Inhaler has been registered since 1996 in several countries. Following the chewing gum, the transdermal patches and the nasal spray, the Nicorette Inhaler was a new form of nicotine administration at the time of registration. Since then, post marketing experience is gained with the Nicorette Inhaler, also in multiple other countries as a non-prescription (over the counter, OTC) product. According to the MAH, unexpected problems did not occur. Several periodic safety update reports have been submitted to the authorities, reporting only few new adverse events.
Because of the similarity of the nicotine inhaler to nicotine chewing gum, which is already available as a non-prescription product, the MAH argued that the classification of the Inhaler should be changed from prescription only to non-prescription. The pharmacology of the Inhaler resembles that of Nicorette gum. The plasma nicotine concentration after use of the Inhaler rises slowly and is comparable to the concentration obtained after use of Nicorette chewing gum. Normal use of the Inhaler will not result in any direct of indirect danger to the user. The Inhaler provides an extra option for self-medication when quitting smoking. The MAH states that since public health policy, social stigmatization and treatment for cessation do not appear to adequately reduce smoking-induced morbidity and mortality, effort should be made to lessen the restricted availability (prescription-only) of the Nicorette Inhaler.

III SCIENTIFIC DISCUSSION

III.1 Quality aspects

Not applicable.

III.2 Non-clinical aspects

No new data have been submitted.

III.3 Clinical aspects

III.3.1 Clinical pharmacology and efficay

No new data have been submitted.

III.3.2 Clinical safety

Update of adverse events in recent/ongoing clinical trials

The expert report reviews 4 recent/ongoing clinical trials, including a placebo-controlled study comprising 221 subjects, an open, controlled 'preference study' where subjects could choose a particular nicotine administration form (115 subjects in each group), a placebo-controlled combination study involving 400 subjects, and an open, controlled smoking-reduction study involving 220 asthmatic smokers. In all studies, the incidence of adverse events (AEs) was not different from other previous studies.

Assessment of clinical safety as reviewed in the expert report submitted by the MAH

The Nicorette Inhaler has been used in clinical trials by approximately 2000 subjects, for various periods of time up to 12 months. In general, AEs have been minor and similar to those reported with the Nicorette chewing gum and patch. No serious AEs have been attributed to the use of the inhaler in clinical trials.

The pharmacological effects of nicotine are well characterized, not only after tobacco smoking but also following administration of nicotine chewing gum, nicotine patch, nicotine nasal spray and the nicotine inhaler. They consist of stimulation of the sympathetic-adrenal system, leading to various hemodynamic and metabolic changes, and include a cholinergic component responsible for psychotropic effects, relaxation of skeletal muscles and an increase in gastrointestinal motility and secretion. These known pharmacological effects may cause clinically relevant adverse events in some subjects, if the plasma nicotine concentration increases to levels higher than those achieved during smoking. If the subject stops smoking completely, the risk of toxicity with inhaled nicotine is low. If the subject continues to smoke while concomitantly using active nicotine replacement therapy (NRT), the risk is theoretically increased, but remains low. Nicotine replacement is given during the initial period of smoking cessation to minimize the tobacco withdrawal symptoms. If the plasma nicotine levels achieved during treatment with NRT are too low, complaints of withdrawal symptoms will occur.
The main local adverse events were throat irritation and coughing, both of which are considered to result from the harsh taste of nicotine. These complaints are mild and transient and normally disappear as subjects adapt to the treatment. None of the adverse events reported were serious enough to be considered as a health hazard, and there were no cases of nicotine toxicity.

Health professionals are of the opinion that the benefits of NRT outweigh the risks involved in continued cigarette smoking. A lit cigarette contains harmful gases and compounds other than nicotine which are known to present a health hazard. Blood nicotine levels achieved with the nicotine inhaler in smoking cessation conditions are lower (one-third) than those observed in chronic cigarette smokers. When nicotine is delivered from the inhaler to the systemic circulation (mostly through buccal absorption) the arterial and venous nicotine levels are initially equal; this contrasts with cigarette smoking, when nicotine is inhaled to the alveoli, resulting in arterial nicotine 'spikes'. Indeed, the initial plasma nicotine levels after smoking (inhaling smoke) are up to 10 times higher in the arteries than in the veins, although this difference disappears after only a few minutes. The lower arterial levels observed with the inhaler reduces the risks of addictiveness and toxicity of nicotine. Pharmacokinetic studies showed that little of the nicotine inhaled from the nicotine inhaler was deposited in the upper respiratory airways and lungs. No pulmonary effects were ever reported during any clinical studies.
Nicotine passes to the fetus and affects its breathing movements and circulation; the effect on the circulation is dose-dependent. Pregnant smokers should be advised to stop smoking completely without using NRT. However, the risk of continued smoking may pose a greater hazard to the fetus compared with the use of NRT products in a supervised smoking cessation program. The Nicorette Inhaler should only be used by pregnant smokers following advice from a physician. Nicotine passes freely into breast milk in quantities that may affect the infant.

Long term use as reviewed in the expert report submitted by the MAH

Interpretation of the reason for long-term use of products with a prescription-only status is difficult. When use is detected at a long-term follow-up, this could be due to the inherent reinforcing effects of the drug but also because of an attempt to extend therapeutic efficacy. Clinical trials with the inhaler recommended subjects to start tapering the use at 3 months and to have ceased usage of the inhaler by 6 months. None of the trials with the inhaler allowed subjects to use the inhaler beyond 6 months, thus the percentage of subjects who would use the inhaler long-term, against advice, is unknown. With nicotine gum, 98% of subjects had stopped using the gum by 1-2 years. Although definitive data are lacking, experience with the nicotine gum suggests that even if long-term use of the inhaler were to occur, use may have ceased within a year. In addition, if long term use were to occur, the health risk associated with continued smoking would be greater.

III.3.3 Post marketing experience reviewed in expert report

Since being launched on the market in September 1996, the Nicorette Inhaler has been marketed in the United Kingdom, USA, Sweden, Denmark, Austria, Italy, Belgium and the Netherlands. There is sufficient exposure of this medicinal product (exact numbers are deleted since this is commercially confidential information).

Adverse events

A complete review of the spontaneous AEs reported from the market (1 September 1996 - 15 June 1998) has been performed and is presented in table E (presented as ADE's).

Table E: Most frequently reported ADEs from spontaneous reports

LOCAL ADE'S	Number of events
Pharyngitis	13
Coughing	8
Stomatitis ulcerative	8
Oedema mouth	4
Pain mouth	4
Irritation in throat	2
Stomatitis	2
Gingival bleeding	2
Gingivitis	2
Moniliasis	2
Pruritus	2
SYSTEMIC ADE's	**Number of events**
Dizziness	9
Headache	9
Vomiting	8
Chest pain	7
Malaise	7
Pain	5
Nausea	4
Insomnia	4
Pain extremities	4
Rash	3
Asthma	3
Dysaesthesia	3
Dyspnoea	3
Sweating increased	3
Taste perversion	3
Allergic reaction	2
Depression	2
Diarrhoea	2
Leg pain	2

Thus further experience, based on a larger population using the Nicorette Inhaler, has not revealed any change in the AE profile or the incidence of AEs compared to that reported previously. No regulatory action has been taken as a result of any adverse events reported during the period 1 September 1996 to 15 June 1998, and there have been no changes in product information as a result of the spontaneous reports received during this period.
According to the MAH, post marketing experience supports the following conclusions:

- The most frequently reported local AEs, from studies and commercial experience, are coughing, throat irritation and sore throat. The most frequently reported systemic AE is headache.
- The incidence of AEs is not correlated with age or gender.
- No serious AE-reports or deaths related to the nicotine inhaler have been reported. Most serious AEs that have been reported in clinical studies have been clinically assessed by the investigator as not causally related to treatment with the inhaler.
- These safety data reflect a very low incidence of AEs associated with the use of the Nicorette Inhaler and support an acceptable safety profile.

Overdose and poisoning
There are no reports of overdose or poisoning associated with the Nicorette Inhaler in clinical studies, post-marketing reports or from the literature. If a child is inadvertently exposed to nicotine by swallowing a cartridge or placing a plug in its mouth, it is likely that the child will develop symptoms of nicotine overdose comparable to the ingestion of one cigarette.

III.3.4 Characteristics of the drug

Abuse potential
The expert report contains argumentation stating that, according to the MAH, the Nicorette Inhaler is expected to have a low abuse/dependence potential similar to that of nicotine gum, and much less than that of cigarettes, based on the following findings:

- nicotine from the inhaler is absorbed from the oral mucosa,
- the rise in blood nicotine levels is slow,
- typical dosing produces venous nicotine blood levels about one-third that of smoking,
- the inhaler produces a minimal rise in "drug liking" and no effects on prototypic ARCI scales to measure abuse liability,
- in clinical trials only 10% of smokers were still using the inhaler at 6 months
- over time, the amount of use/day declines, and
- there are few adverse event reports suggestive of abuse/dependence.

Potential for harm from inappropriate use
According to the expert report of the MAH, inappropriate use of the Inhaler is not likely to cause harm because:

- The inhaler delivers a lower dose of nicotine than that a smoker would obtain from cigarettes, without the extraneous toxic components in cigarette smoke.
- Intensive use of the inhaler has resulted in mean nicotine plasma concentrations that are similar to those obtained from cigarette smoking.
- There has been no evidence that inappropriate use is a problem with the inhaler. Between being first marketed in September 1996, to 15 June 1998, there have been no reports of accidental or deliberate ingestion of nicotine cartridges. The inhaler mouthpiece has been specifically designed to make it difficult for a child to pull apart the inhaler and so get to the cartridge inside.
- There is no evidence from the market that the nicotine inhaler is being abused by either children or non-smokers.
- Clinical data and marketing experience indicate that there is a tendency for consumers to use the inhaler at the lower end of the dosage recommendation (i.e. 6 inhalers/day).
- Minimizing inappropriate use of the Nicorette inhaler has been addressed through the product labeling. In addition, material to assist pharmacists when counseling smokers is provided.
- Although nicotine in high doses can potentially be harmful, the possible consequences of harm from inappropriate use of the inhaler are much less than the dangers of continuing to smoke.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The assessor concluded that the compound is safe with little benefit concerning efficacy. Usage of the Nicorette Inhaler results in slow rising of nicotine plasma levels and demonstrates a low peak plasma profile, similar to Nicorette chewing gum. The chewing gum has a non-prescription status. Hence, considering the similar bioavailability of nicotine from the two products and the knowledge on safety, the Nicorette Inhaler can be granted a non-prescription status too. Although there is a general existing regulatory restriction that inhalers are not allowed as non-prescription products, the MEB concluded on 18 October 1999, based on the data on safety, that the variation application for Nicorette Inhaler 10 mg for a change of the prescription status from prescription-only to non-prescription is approvable.

IV.1 Product information

Patient Information Leaflet (PIL)
The MAH incorporated some changes in the PIL to contribute to a safer and more effective use of the Inhaler. Changes included advice to consult a doctor when using other medicines or when suffering from other medical conditions.
The MEB assessed the updated PIL and approved the text with several small adjustments. One statement had to be removed from the PIL, as it was considered to be for marketing purposes.

Labeling of the packaging
Upon approval of the non-prescription status, the packaging size changed to a starting set containing 6 cartridges and a refill-packaging set containing 18 cartridges. As required for non-prescription products, the updated labeling contains information on the indication and excipients. The MAH suggested to include the same information as presented on the packaging of other non-prescription Nicorette products. This was accepted by the MEB.

Annex II – Extension of the indication to "Relieving or treating severe nicotine withdrawal symptoms when quitting smoking".

I RECOMMENDATION

Based on the review of the available data, the MEB considers that the variation application for Nicorette Inhaler 10 mg for an extension of the indication to "Relieving or treating severe nicotine withdrawal symptoms during quitting smoking" is approvable.

Major objections have been solved and the product information has been amended accordingly.

II EXECUTIVE SUMMARY

II.1 Scope of the variation

In December 2000, the MAH submitted a Type II variation for Nicorette Inhaler 10 mg via a national procedure. The aim of the application was to extend the indication to "Relieving or treating severe nicotine withdrawal symptoms", thereby including use of the Nicorette Inhaler as a replacement for smoking in situations where smoking is not allowed or not favorable.
During the procedure, the MAH changed the sought indication to "Treatment of tobacco dependence by relieving nicotine withdrawal symptoms, thereby facilitating smoking cessation in smokers motivated to quit. Even though complete smoking cessation is preferable, this medicinal product can be used when a smoker abstains from smoking temporarily". The MAH submitted data from one additional study to support the application.

II.2 Supplementary paragraph

The MAH argued that despite extensive campaigns to stop smoking and the over the counter availability of Nicorette products, a large percentage of smokers is still not able to stop smoking. This is hazardous to their own health but also causes a significant risk to other people, for example young children and people with conditions such as chronic non-specific respiratory disease (CNSRD) and chronic obstructive pulmonary disease (COPD). Reduction of the number of cigarettes smoked would reduce the hazard for people surrounding the smoker. By relieving or treating severe nicotine withdrawal symptoms, the MAH claims that the Nicorette Inhaler is able to help a smoker not smoking in situations where it disturbs or endangers the surrounding or where smoking is not allowed (anti-smoking policy in the workplace in the Netherlands since February 2001). Although it is preferred that smokers try to quit smoking, the use of nicotine replacing products like the Nicorette Inhaler in situations where smoking is not allowed, will provide a smoker with familiarity and knowledge about the function and efficacy of the inhaler. This increases confidence in the product; which will more likely result in an attempt to quit smoking, according to the MAH.

III SCIENTIFIC DISCUSSION

III.1 Quality aspects

Not applicable.

III.2 Non-clinical aspects

No new data have been submitted.

III.3 Clinical aspects

To support the application for the indication “Relieving or treating severe nicotine withdrawal symptoms”, the MAH submitted data of one cross-over study including 50 subjects. The MEB decided that the number of subjects included in the study was insufficient. There were also concerns regarding the methodology. It was unclear why a ‘cross-over’ design was used instead of a ‘parallel’ study design which would have decreased the risk for ‘carry over’ effects. In addition, all clinical study data assessed at the time of registration was based on the principle that subjects stopped smoking before using the Nicorette Inhaler. One extra study with 50 subjects is considered insufficient for the applied extension of the indication.

In addition to the above, extension of the indication was also rejected based on the following argumentation.

- The originally accepted indication regards relieving or treating nicotine withdrawal symptoms after a person stops smoking. It is now proposed to use the product for alleviating nicotine withdrawal symptoms when there is the urge to smoke, so outside a stop-smoking program. Such application eliminates the incentive to stop smoking, which is not acceptable.
- In the presented clinical trials, patients were requested to not smoke for 10 hours before administration. Subsequent treatment was 2 to 3 days. These study conditions do not correspond with the circumstances as they appear from the amended indication. Situations with an "urge to smoke" will often occur without time limitation, unless smoking is stopped completely. Accordingly, short term or long term efficacy for the amended indication has not been demonstrated with the submitted clinical studies.
- In addition to the above, short term or long term safety for the amended indication has not been demonstrated with the submitted clinical studies.

In the response phase of the procedure, the MAH stated that it is not the intention to eliminate the incentive to stop smoking. Therefore, the MAH suggested to formulate the indication similar to the indication in another European country: *"Treatment of tobacco dependence by relieving nicotine withdrawal symptoms, thereby facilitating smoking cessation in smokers motivated to quit. Even though complete smoking cessation is preferable, this medicinal product can be used when a smoker abstains from smoking temporarily".*

The rephrased indication was rejected since the objections raised by the MEB during the first round were not solved by the proposed adjustment of the indication. However, the MEB considered the following change in indication acceptable: “Relieving or treating severe nicotine withdrawal symptoms upon quitting smoking” to “Relieving or treating severe nicotine withdrawal symptoms when quitting smoking”. In the latter, interpretation of ‘when’ as ‘in the process of quitting smoking’ is accepted.

IV OVERALL CONCLUSION

The indication “Relieving or treating severe nicotine withdrawal symptoms when quitting smoking” was approved. With this, the procedure was finalized on 4 January 2002 and the product information was adjusted accordingly.