

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Nicorette Invisi pleister 10 mg, transdermal patch 10 mg/16 hours
Nicorette Invisi pleister 15 mg, transdermal patch 15 mg/16 hours
Nicorette Invisi pleister 25 mg, transdermal patch 25 mg/16 hours
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 34968-34970

7 March 2013

Pharmacotherapeutic group:	drugs used in nicotine dependence
ATC code:	N07BA01
Route of administration:	transdermal
Therapeutic indication:	relief of nicotine withdrawal symptoms in the treatment of nicotine addiction
Prescription status:	non prescription
Date of authorisation in NL:	25 October 2010
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

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

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Nicorette Invisi pleister 10 mg, transdermal patch 10 mg/16 hours, Nicorette Invisi pleister 15 mg, transdermal patch 15 mg/16 hours and Nicorette Invisi pleister 25 mg, transdermal patch 25 mg/16 hours from Johnson & Johnson Consumer B.V. The date of authorisation was on 20 October 2010 in the Netherlands.

The product is indicated for relief of nicotine withdrawal symptoms in the treatment of nicotine addiction.

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

Nicotine has no therapeutic uses except as replacement therapy for the relief of abstinence symptoms in nicotine-dependent smokers.

Owing to its many actions, the overall effects of nicotine are complex. A wide variety of stimulant and depressant effects are observed that involve the central and peripheral nervous, cardiovascular, endocrine, gastro-intestinal and skeletal motor systems. Nicotine acts on specific binding sites or receptors throughout the nervous system.

This national procedure concerns line extension to Nicorette 5 mg, Nicorette 10 mg and Nicorette 15 mg transdermal patches (NL License RVG 15599-15601), which have been registered by Johnson & Johnson Consumer B.V. since 1993.

A new strength of 25 mg is added. Moreover, the applications concern a new patch technology. The new nicotine transdermal patch (NNTP) consists of a precoated backing layer, a nicotine source layer and a skin contact adhesive layer with print on the patch in light brown ink. The reference products are larger than NNTP and opaque. The NNTP makes it possible to increase the starting dose of the patch from 15 mg to 25 mg due to its surface area. The regular Nicorette patches contain 0.83 mg nicotine/cm², whereas the Invisible patches contain 1.75 mg nicotine/cm². The patch size of the Invisi patch is thus about 50% smaller compared to equipotent doses of the regular Nicorette patch. Other high dose patches that are available on the Dutch market are Nicotinell 21 mg/24 hr, and NiQuitin 21 mg/24 hr.

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 Invisi 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 dossiers of Nicorette 5 mg, 10 mg and 15 mg patches. To support the application, the MAH has carried out a study to examine the use of higher doses (25 mg Nicorette® patches) in heavy smokers (> 15 cigarettes a day) (CEASE study). Three pharmacokinetic studies were conducted. The aim of study NICPAT-9145-002 was to investigate the relationship between the released nicotine dose from the new nicotine transdermal patch (NNTP) area in comparison to Nicorette patches. In study NICPAT-9145-003 the dose proportionality was evaluated, and in study NICPAT-9145-004 the bioequivalence between the new nicotine transdermal patch (NNTP) and the marketed Nicorette patch was evaluated. The results of the studies 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 colourless or brownish viscous liquid which is volatile and hygroscopic, soluble in water and miscible with alcohol. Nicotine has one chiral centre and is produced as the S-(-)-isomer.

Manufacturing process

The MEB has been assured that the manufacturing process is adequately controlled and validated.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and additional specifications. Batch analytical data demonstrating compliance with this specification have been provided.

Stability of drug substance

For the active substance a retest period of 4 years is applicable when stored under the stated conditions.

* *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 Invisi pleister 10 mg, 15 mg and 25 mg are transdermal patches sized 9.0 cm², 13.5 cm² and 22.5 cm², respectively. Each patch contains 1.75 mg nicotine/cm². The drug products are dose-proportional.

The patches are semi-transparent, beige, imprinted, rectangular transdermal therapeutic system (TTS) with rounded corners, centrally located on a rectangular, aluminized and siliconized release liner. Each pouch is labelled with medicinal name, strength and pharmaceutical form.

The transdermal patches are packed in heat-sealed four seamed laminate pouches consisting (from outside to inside) of paper, PET, aluminium and acrylnitrilcopolymer.

The excipients are: medium-chain triglycerides, basic butylated methacrylate copolymer, potassium hydroxide (E525), croscarmellose sodium (E468), polyethylenterephthalate film, single side aluminised polyethylenterephthalate film.

The excipients in the nicotine matrix are commonly used in transdermal therapeutic systems. The same applies for acrylic adhesive solution and PET.

Pharmaceutical development

The development of the product is satisfactory performed and explained. The excipients used are common in the manufacture of transdermal systems. Nitrogen is used to displace air during manufacturing of the drug product. The packagings are usual and suitable for the product at issue. The formulation used in the clinical trials is, apart from the size of the experimental patch sizes, identical to that proposed for marketing.

Manufacturing process

The manufacturing process consists of the following steps: manufacture of the non drug-containing acrylic laminate, manufacture of the nicotine mass, coating/laminating of nicotine mass to form final laminate and finally the patches are punched from final laminate. The in-process controls and controls of process parameters are deemed acceptable. The MAH has adequately validated the manufacturing process.

Control of excipients

Most excipients comply with the Ph.Eur. The in-house specifications for aluminium acetylacetonate, acrylic adhesive solution and PET (backing layer and release liner) are acceptable. Moreover, adequate specifications have been included for the process liners and printing colours/ink.

Quality control of drug product

The product specification for the patch includes tests for appearance, identity, assay, uniformity of dosage forms, degradation, uniformity of dosage units, *in-vitro* release, adhesive strength, peel force, pouch tightness, residual solvents and microbiological purity. The limits are considered acceptable. Batch analysis data have been provided on three batches. Compliance with the release requirements is demonstrated.

Stability of drug product

The patches have been stored at 25°C/60% RH (48 months), 30°C/65% RH (48 months) and 40°C/75% RH (6 months). All batches are production scale and produced using final equipment. Adequate photostability studies have been performed. Degradation was observed for the samples irradiated directly on to the matrix after the release liner was removed. However, the patches irradiated on the aluminized release liner or transparent backing foil did not show changes concerning degradation products. Therefore, no additional labeling statement regarding protection for light needs to be included. Based on the data provided, a shelf-life of three years was granted. The product should be stored below 25°C.

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

These products are line extensions to Nicorette 5 mg, 10 mg and 15 mg transdermal patches. The MAH provided an expert report on the relevant studies and reviewing critical issues. The scope of the assessment was limited to non-clinical safety studies, an evaluation of the safety of the degradants and impurities of nicotine, residual solvents as well as excipients in the New Nicotine Transdermal Patch (NNT) used in the treatment of tobacco dependence.

Pharmacodynamics/pharmacokinetics

The pharmacology of nicotine has previously been discussed in earlier submissions, and was not reassessed. No new pharmacokinetic studies in animals were performed.

Toxicology

Single dose toxicity

No new studies have been performed. In Beagle dogs, 6 Nicorette patches (149.4 mg of nicotine; 19.2-19.7 mg/kg) percutaneously for 18 hours were found to be non-lethal, but caused salivation and were emetogenic.

Repeated dose toxicity

No new studies have been performed. The NOAEL (No Observed Adverse Effect Level) in Beagle dogs from an earlier study with Nicorette patches was estimated to be 24.9 mg/animal/day.

Reproduction studies/mutagenic potential/Oncogenic and carcinogenic potential

No new studies have been performed.

Local tolerance

Repeated administration of the NNTP to rabbit skin causes severe irritation. Similar results were obtained with the existing Nicorette patches. Yet, temporal differences in the occurrence of severe erythema suggest a greater potential of the NNTP as compared with the original Nicorette patches. However, clinical data showed acceptable compatibility for the NNTP patch compared to the original Nicorette patch when the number of adverse events is considered. However, when skin irritation is scaled, the NNTP patch scores higher than the original patch. The clinical findings are thus somewhat mixed. For this reason and because of the clear findings in rabbits, the non-clinical findings are reflected in the SPC.

Special toxicity studies

Sensitising potential

No new studies on the sensitising potential of NNTP were performed. In previous studies, nicotine or the Nicorette® Patch showed no delayed contact hypersensitivity reaction. Also the Nicorette® Patch was judged to be negative in the skin photosensitization test.

Impurities, degradants and excipients

Impurities, degradants and excipients were discussed by the MAH. From a toxicological point of view the proposed limits for impurities and degradants and the use of the proposed excipients are all acceptable.

Environmental risk assessment

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

II.3 Clinical aspects

Nicotine is a well-known active substance with established efficacy and tolerability. In support of the application the MAH submitted three pharmacokinetic studies and a study to examine the use of higher doses (25 mg Nicorette® patches) in heavy smokers (> 15 cigarettes a day) (CEASE study).

II.3.1 Clinical pharmacokinetics

Three pharmacokinetic studies were submitted. In study NICPAT-9145-002 the relationship between the released nicotine dose to the new nicotine transdermal patch (NNTP) area was evaluated in comparison to original Nicorette patches. In study NICPAT-9145-003 the dose proportionality was evaluated, and in study NICPAT-9145-004 the bioequivalence between the new nicotine transdermal patch (NNTP) and the marketed Nicorette patch was evaluated.

NICPAT-9145-002

This was an open label, single dose, randomized, crossover study in 12 healthy smoking subjects. Subjects smoked a minimum of 15 cigarettes/per day for at least one year.

The primary objective of the study was to define patch areas of the new nicotine patch that correspond to the 10 mg/16h, 15 mg/16h and 25 (10+15) mg/16h Nicorette patches. Five patch areas of the new nicotine patch were chosen, three of which were believed to deliver similar amounts of nicotine as the three Nicorette patches. In addition one patch believed to deliver less nicotine than the lowest Nicorette patch and one believed to deliver more nicotine than the highest Nicorette patch were chosen.

The following treatments were applied:

- A: Nicorette patch 20 cm², 10 mg/16h
- B: Nicorette patch 30 cm², 15 mg/16h
- C: Nicorette patch 50 cm², 25 mg/16h (Nicorette patch 20 cm², 10 mg / 16h + Nicorette patch 30 cm², 15 mg /16h
- D: NNTP 10 cm², 8 mg/16 h

E: NNTP 16.3 cm², 13 mg/16 h
 F: NNTP 22.5 cm², 18mg/16 h
 G: NNTP 28.8 cm², 23 mg/16 h
 H: NNTP 35 cm², 28 mg/16 h
 I: placebo Nicorette patch (20 cm² + 30 cm²)
 H: placebo NNTP 35 cm²

The patches were applied at the left and right arm (upper and lower part) and the left and right hip (lateral and medial side). After removal the patches were analysed for the residual nicotine. The delivered amount of nicotine is listed in table PK 1.

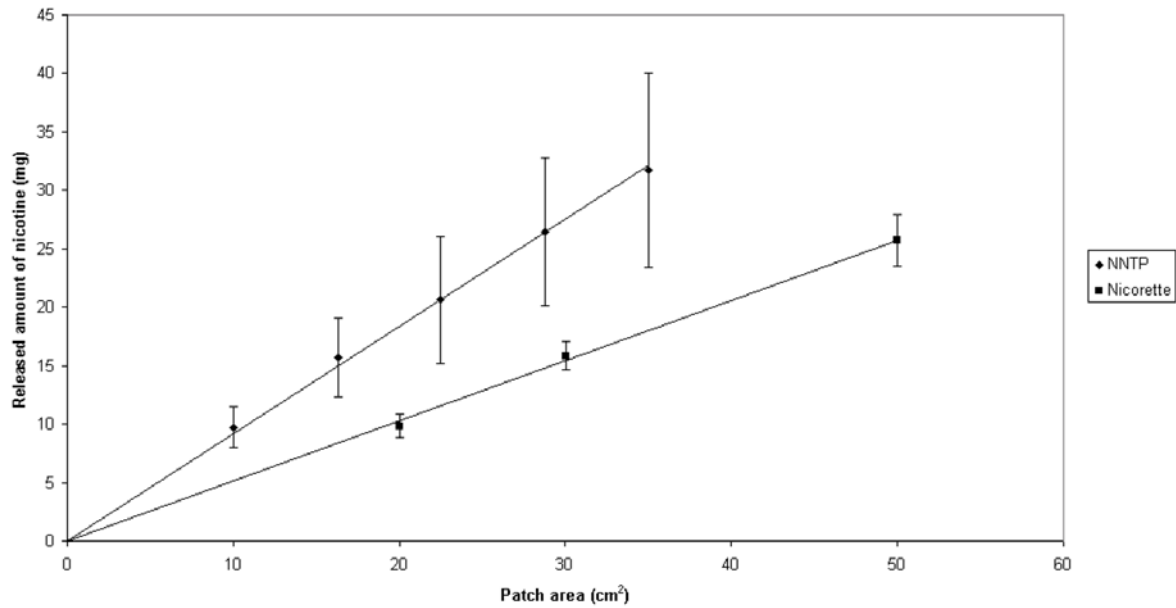
Table PK 1. Delivered amount of nicotine after patch application for 16 hours.

Variable	Treatment							
	Nicorette (patch area – cm ²)			NNTP (patch area – cm ²)				
	20	30	50	10	16.3	22.5	28.8	35
n	12	12	12	12	11	12	12	11
mean	9.8	15.9	25.7	9.7	15.7	20.6	26.5	31.7
median	9.9	15.6	25.9	9.7	16.5	20.7	26.0	30.6
stdev	1.0	1.2	2.2	1.8	3.4	5.5	6.3	8.3
min	7.9	14.1	21.1	6.6	7.4	11.7	16.3	15.8
max	11.3	17.9	29.2	13.7	19.7	29.7	38.2	45.0

A clear relationship was shown for the released amount of nicotine vs. the patch area for both patches (see figure PK 1). During the application the new patch release more nicotine per cm² compared to the Nicorette patch.

Figure PK 1. Released amount of nicotine vs. patch area (mean ± s.d.; patch application - 16 Hours)

Released amount of nicotine versus patch area
(mean ± stdev; patch application - 16 hours)

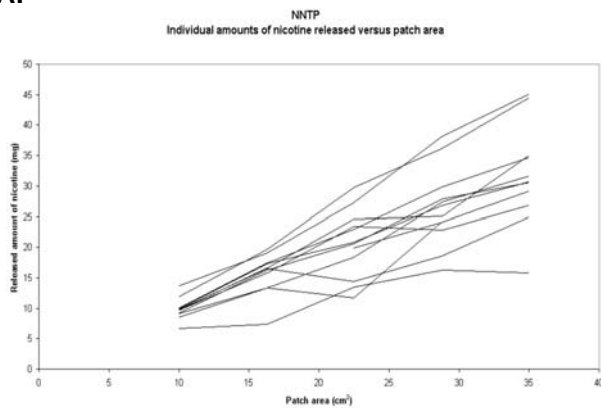


The linear equation for released amount of nicotine versus patch area for NNTP was $y=1.1149+0.8758*x$. Using this equation the NNTP areas corresponding to the Nicorette patches delivering 10 mg, 15 mg and 25 mg/16h would be 10.1cm², 15.9 cm² and 27.3 cm², respectively.

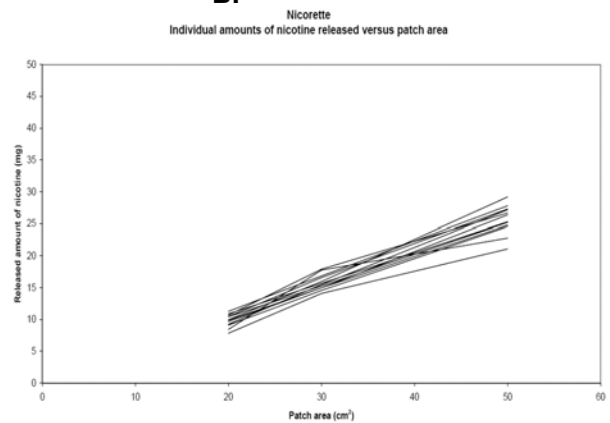
As shown in Figure PK 2 A and B, the variability in nicotine release is pronounced higher for the new patch compared to Nicorette. The MAH indicated that this may be caused to the fact that the new patch (NNTP) was produced in a laboratory scale while the Nicorette patch is produced at an industrial scale.

Figure PK 2. A: NNTP - Individual amounts of nicotine released vs. patch area, and B: Nicorette - individual amounts of nicotine released vs. patch area

A:



B:



NICPAT-9145-003

This was an open label, single dose, randomized, crossover study in 18 subjects. Subjects smoked a minimum of 15 cigarettes/per day for at least one year. The primary objective of this study was to demonstrate linear pharmacokinetics of nicotine after application of two patch formulations, the Nicorette patch 10, 30 and 50 (20 + 30) cm² and the New Nicotine Transdermal Patch (NNTP) 10.0, 22.5 and 35.0 cm².

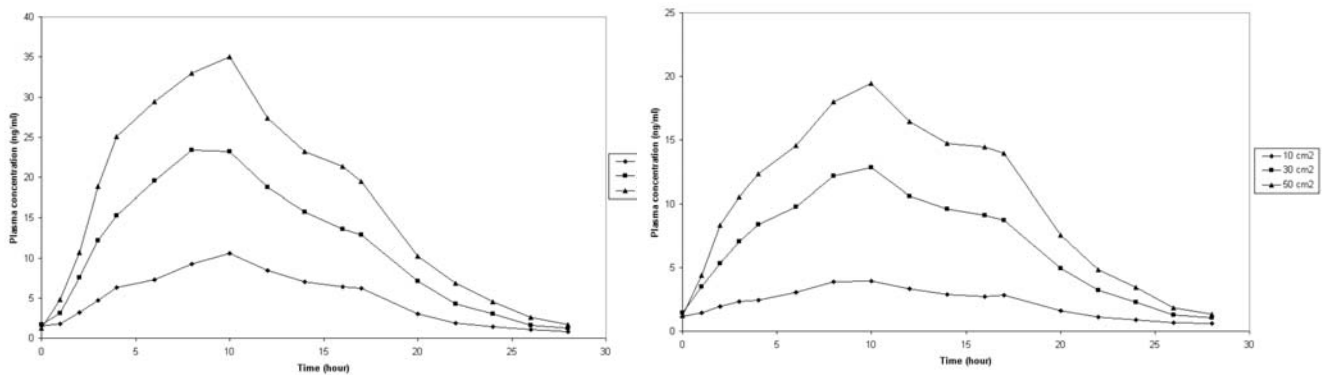
In order to minimize the risk of skin irritation the patches were applied on different positions (medial, lateral, upper and lower part of right or left hip). Each patch was applied for 16 hours. Blood samples were collected for 28 hours after patch application. The following pharmacokinetic parameters were calculated: C_{max}, AUC_{inf}, AUC_{16h}, AUC_{24h}, t_{max} and t_{1/2}. The results are listed in table PK 2 and Figures 3 A and B.

Table PK 3. Pharmacokinetic variables of nicotine (± SD) after patch application for 16 hours.

Treatment	Dose (mg)	C _{max} (ng/ml)	t _{max} (h)	AUC _{inf} (h*ng/ml)
Nicorette® 10cm ²	5.0 ± 0.4	4.1 ± 1.0	9 ± 2	60 ± 14
Nicorette® 30cm ²	16.3 ± 1.6	14.3 ± 3.4	10 ± 4	194 ± 48
Nicorette® 50cm ²	25.9 ± 1.7	21.3 ± 5.4	11 ± 4	299 ± 86
NNTP 10cm ²	10.8 ± 1.8	11.0 ± 4.0	9 ± 2	140 ± 51
NNTP 22.5cm ²	24.9 ± 3.9	25.2 ± 8.0	9 ± 2	327 ± 118
NNTP 35cm ²	37.1 ± 7.7	37.0 ± 13.4	9 ± 3	494 ± 185

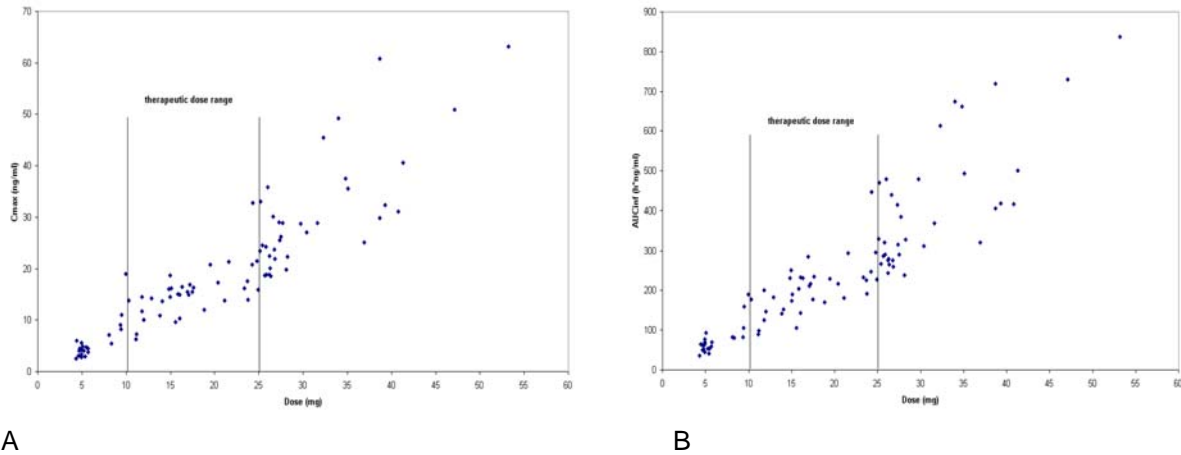
Figure 3. Nicotine plasma concentrations after application of the NNTP (A) and Nicorette patches for 16 hours (B).

A: NNTP:



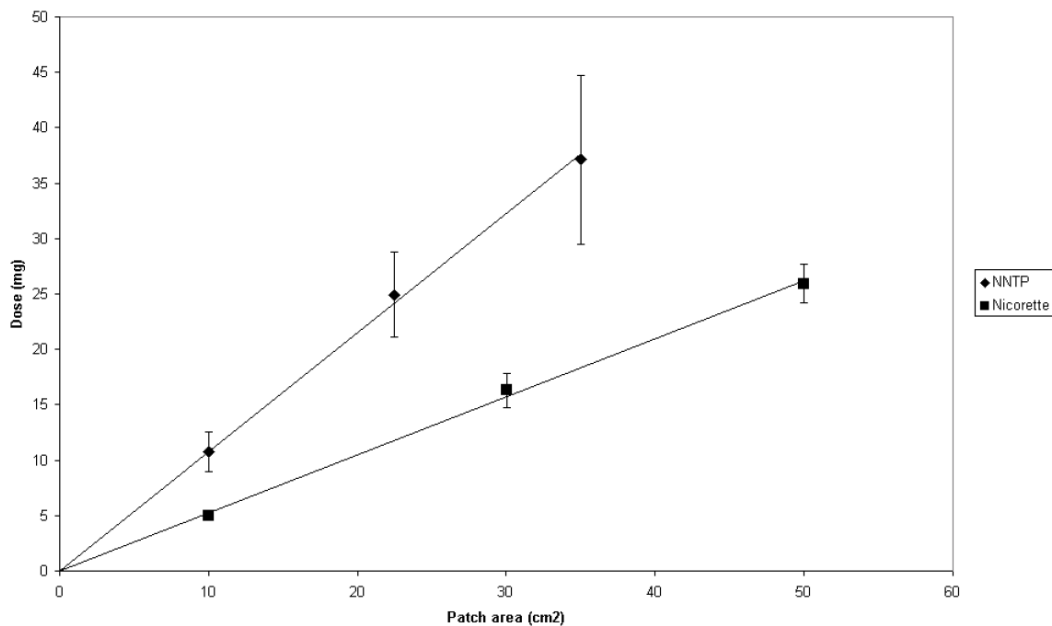
For each individual patch formulation, as well as when data from both formulations were combined, there was a strong linear relationship between released amount of nicotine (dose) and C_{max} and AUC_{inf} (but also for AUC_{16h} and AUC_{24h}; no shown) (Figure 4 A and B) over the therapeutic dose range (10 – 25 mg/16h) as well as over the entire dose range tested (5 – 37 mg/16h).

Figure PK 4. Relationship between C_{max} vs. dose (A) and AUC vs. dose (B).



A clear relationship was shown for the released amount of nicotine vs. the patch area for both patches (see figure PK 5). As can be observed from the SD values in table PK 3 a higher variability for the NNTP formulation is observed than for Nicorette.

Figure PK 5. Released amount of nicotine vs. patch area (mean ± s.d.; patch application - 16 Hours)



NICPAT-9145-004

This study evaluated the bioequivalence between Nicorette and the new nicotine patch (NNTP). 28 subjects, smoking a minimum of 15 cigarettes/per day for at least one year, could be included in the evaluation. Nicorette 50 cm² (20 + 30 cm²; total release rate 25 mg/16h) was compared with NNTP 22.5 cm² (release rate 25 mg/16h). The pharmacokinetics are shown in table PK 3 and the C-t curves in figure PK 6.

Table PK 4. Pharmacokinetic variables of nicotine after application of Nicorette 50 cm² (20 + 30 cm²; total release rate 25 mg/16h) and NNTP 22.5 cm² (release rate 25 mg/16h) (n=28).

Treatment	Dose (mg)	C _{max} (ng/ml)	t _{max} (h)	AUC _t (h*ng/ml)	AUC _{inf} (h*ng/ml)
Nicorette®	26.6 ± 1.6	21.8 ± 3.7	9 ± 2	299 ± 52	311 ± 53
NNTP	26.7 ± 3.8	24.2 ± 5.4	9 ± 2	300 ± 68	311 ± 71

Figure 6. Nicotine plasma concentrations after application of the NNTP and Nicorette patches for 16 hours.

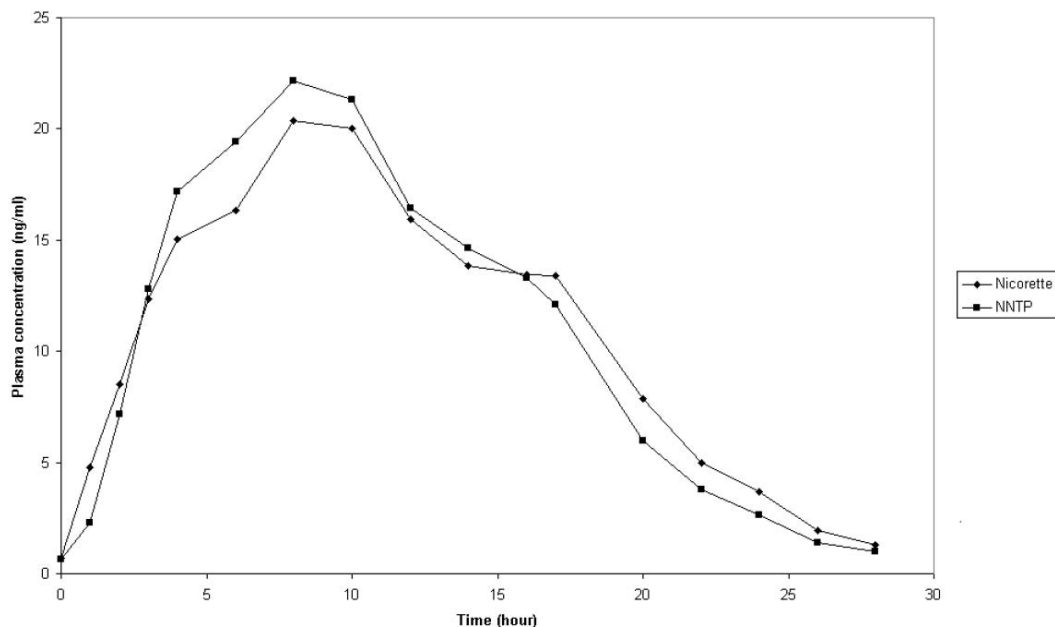


Table PK 5. Statistical evaluation of the pharmacokinetic variables.

Parameter	μ_{ref} / μ_{test} geometric mean (90% CI)
C _{max}	1.10 (1.02 – 1.19)
AUC _t	0.99 (0.92 – 1.07)
AUC _{inf}	0.99 (0.92 – 1.06)

Based on the results provided, bioequivalence is considered demonstrated for Nicorette and the NNTP patch (see table PK 4 and PK 5).

Conclusion and discussion

The new patches (NNTP) release more nicotine per cm² compared to Nicorette patches. In study NICPAT-9145-002, a linear relationship of the released amount of nicotine vs. the patch area over the 10 – 35 cm² range was observed. Using this relationship it was estimated that the NNTP areas corresponding to the Nicorette patches delivering 10 mg, 15 mg and 25 mg/16h would be 10.1 cm², 15.9 cm² and 27.3 cm², respectively. Although in study NICPAT-9145-003 also a linear relationship was observed, it appeared that the release rate from the NNTP in this study was higher than that observed in study NICPAT-9145-002. According to the MAH this was due to the fact that in the first study the patches were manufactured at laboratory scale, and in the second study at industrial scale. The results from both studies indicate that the desired release rate was obtained with the smaller patch sizes, and that the AUC and C_{max} increased linear with the dose (and patch size).

Although a higher variability was observed for the NNTP, bioequivalence was proven in study NICPAT-9145-004, in which Nicorette 50 cm² patches (20 + 30 cm²; total release rate 25 mg/16h) were compared with NNTP 22.5 cm² (release rate 25 mg/16h; industrial scale). Taking into account that the release rate is directly related to the patch size for the Nicorette patch as well as for the NNTP, to obtain a comparable release rate for the NNTP with Nicorette 20 cm² (10 mg/16h) and Nicorette patch 30 cm² (15 mg/16h) the patch size of the new patch should be 9 cm² (10/25 * 22.5 cm²) and 13.5 cm² (15/25 * 22.5 cm²), which is agreed.

II.3.2 Clinical experience

Methodology

No efficacy study was conducted with the NNTP formulation. Only one study was conducted to examine the use of higher doses in heavy smokers. This study (the CEASE study or study 93-NNPA-004) was conducted in 1994 -1995 with Nicorette® patches.

As no clinical studies were performed with the NNTP formulation the safety of the new formulation was uncertain. In relation to this concern the MAH submitted results of local tolerability studies performed with the new Invisi formulation in smoking volunteers. As for the highest strength (25 mg), local tolerability scores were comparable to placebo, and as the local tolerability scores were mild for the two highest strengths (15 & 25 mg/16h), the new patch is acceptable. The safety of the NNTP formulation of Nicorette patches in the study is sufficiently demonstrated.

The results of the CEASE study are used to evaluate the efficacy and safety of Nicorette® patches dosed at 25 mg per day compared to 15 mg per day in heavy smokers, specifically whether the higher dose leads to higher rates of smoking cessation and whether this higher dose is well tolerated. Another purpose of the study was to investigate whether longer treatment duration (8 vs. 22 weeks) increases smoking cessation rates.

This randomised controlled trial recruited 3,575 heavy smokers, where heavy smoking was defined as more than 15 cigarettes per day, who were motivated to stop smoking. In addition, subjects had to smoke for at least three years, had at least one failed attempt at smoking cessation and be between 20 and 70 years old. Smokers with a myocardial infarction within the last three months or who were under psychiatric care or medication, or with an alcohol or any other drug problem were excluded.

Smokers were randomised into one of five treatment arms:

- 25 mg Nicorette® patch for 22 weeks (n=715)
- 15 mg Nicorette® patch for 22 weeks (n=715)
- 25 mg Nicorette® patch for 8 weeks (n=715)
- 15 mg Nicorette® patch for 8 weeks (n=716)
- placebo (n=714)

All subjects used two patches per day. Subjects in the 25 mg group received per day one large patch (30 cm²) which provided 15 mg nicotine and one small patch (10 cm²) which provided 10 mg nicotine. Subjects in the 15 mg group received per day one large patch (30 cm²) which provided 15 mg nicotine and one small patch (10 cm²) which provided placebo. Subjects in the placebo group received per day one large and one small placebo patches.

Subjects in the 15 mg nicotine group received about 1 mg nicotine per hour; the 25 mg group received approximately 1.56 mg nicotine per hour.

Subjects were instructed to apply the patches in the morning and remove them at bedtime.

The patches were worn for 16 hours per day. The rationale for developing a patch to be worn for 16 hours and removed prior to going to bed was to reduce sleep disturbances that have been reported with the use of nicotine patches for 24 hours. The 16 h wear time has been accepted before for a similar product (Nicorette patch).

Because the new patch is bioequivalent to the Nicorette patch over a wearing period of 16 hours, the 16-hr wear period is thus acceptable. No excessive harm is expected when the patches would be worn for 24 hours or more. In two repeat dose (21 days) studies assessing local irritancy, the NNTP was worn for 24

hours. But this did not lead to significant safety problems. Moreover, the pharmacokinetic studies indicated that nicotine release is less after 16 hours.

The 25 mg groups were tapered off for two weeks on 15 mg and two weeks on 10 mg nicotine patches. The 15 mg groups were tapered off for four weeks on 10 mg patches.

The primary efficacy outcome was based on self-reported smoking status, biochemically verified by expired carbon monoxide (CO) < 10 ppm. Successful smoking cessation was defined as continuous abstinence from visit three (week two) until week 52. All subjects with missing data or lapses were defined as treatment failure.

Efficacy

Patient disposition in the five treatment arms are presented in the figure below.

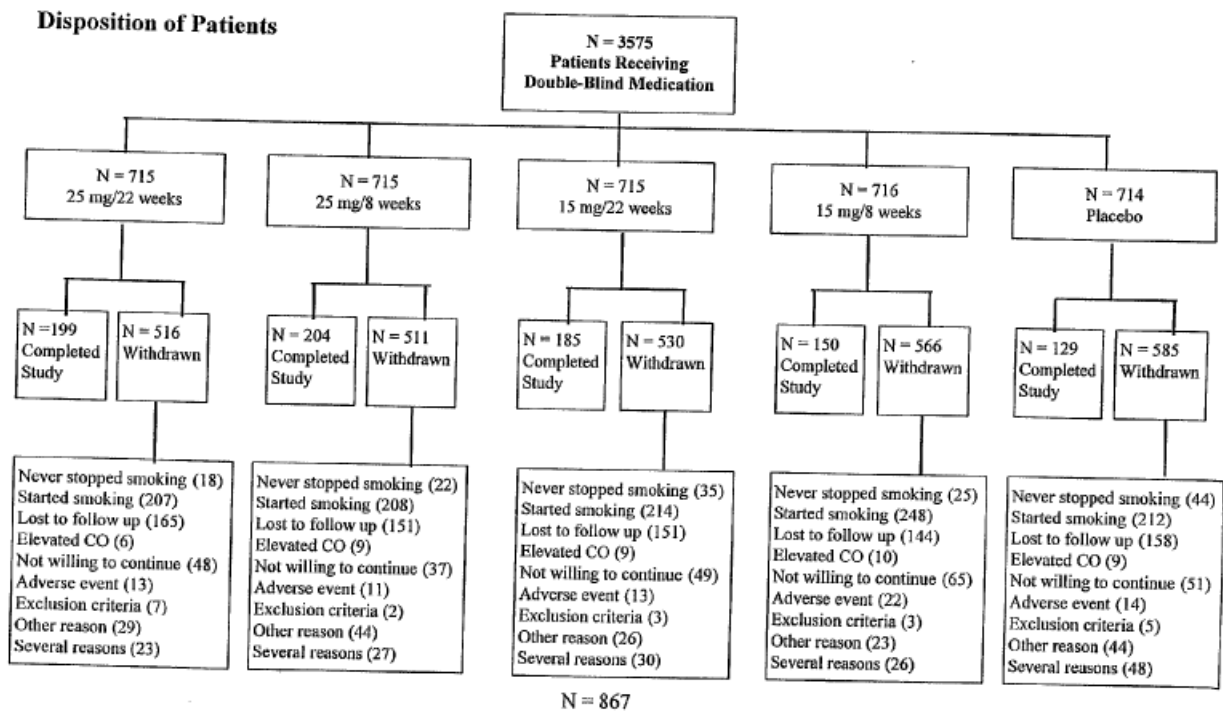


Fig. 5. Patients Completing Study

Since a large proportion of subjects were withdrawn from the study during the 1-year follow-up, any assumption made about these subject, specifically the assumption that all withdrawal are treatment failure, may have a biasing effect on the study results, especially if the proportion of withdrawal is differentially distributed across the dose group. In order to address this possibility, the proportion of patients dropping out in each treatment group were calculated based on the figures presented above, referring to patients disposition. The results are presented in the table below.

	25mg/22 weeks	25mg/8 weeks	15mg/22 weeks	15mg/8 weeks
N	715	715	715	716
withdrawn	516	511	530	566
% withdrawn	72%	71%	74%	79%
Never stopped smoking	18	22	35	25
Started smoking	207	208	214	248
Elevated CO	6	9	9	10
Total withdrawn due to smoking	231	239	258	283
% withdrawn due to smoking	32%	33%	36%	40%
% withdrawn due to other reasons	40%	38%	38%	40%

The results in the table above indicate that indeed a larger proportion of patients were withdrawn from the lower dose groups (15 mg) than from the higher dose groups (25 mg). However, this difference is due to subjects who withdrew due to smoking (i.e. never stopped smoking or started smoking). The proportion withdrawn due to other reasons is identical across the two dose groups. Therefore it is concluded that the assumption made about withdrawals is not very likely to have produced a bias.

The continuous abstinence rates (self-reported and corroborated by CO < 10) in the five treatment arms over time are presented in the table below.

Table 9

Continuous self reported complete abstinence from week two until endpoint together with a CO measurement of less than 10 ppm by treatment

Visit	25 mg/ 22 weeks		25 mg/ 8 weeks		15 mg/ 22 weeks		15 mg/ 8 weeks		Placebo	
	N	%	N	%	N	%	N	%	N	%
Week 2	524	73.3	538	75.2	489	68.4	485	67.7	352	49.3
Week 4	355	49.7	362	50.6	308	43.1	293	40.9	198	27.7
Week 8	264	36.9	292	40.8	232	32.5	209	29.2	148	20.7
Week 12	218	30.5	243	34.0	195	27.3	169	23.6	125	17.5
Week 22	159	22.2	171	23.9	142	19.9	124	17.3	94	13.2
Week 26	140	19.6	150	21.0	132	18.5	110	15.4	87	12.2
Week 52	110	15.4	114	15.9	98	13.7	84	11.7	71	9.9

Statistical testing indicated that the abstinence rate was significantly higher for the combined group of all active treatment compared to placebo.

When the four treatment groups were combined according to treatment duration (8 weeks vs. 22 weeks), the results indicate no difference in smoking cessation rates rate between the two treatment durations at any time while there were persistent differences between the groups defined by dose.

The table below indicates that the proportion of subjects with continuous abstinence in the combined 25 mg groups (n=1430) was significantly higher than in the combined 15 mg group throughout the study. The proportion of subjects who were continuously abstinence from visit three (week two) until week 52 was 15.7% in the 25 mg group compared to 12.7% in the 15 mg group (difference of 3% with a 95% CI: 0.4 – 5.5).

Table 11
Continuous self reported complete abstinence from week two until endpoint verified by exhaled CO < 10 ppm by dose

Visit	25 mg	15 mg	Placebo	CI 25mg - 15 mg	P-value 25mg vs 15 mg
Week 2	74.3	68.1	49.3	2.9, 9.5	< 0.005
Week 4	50.1	42.0	27.7	4.5, 11.8	< 0.005
Week 8	38.9	30.8	20.7	4.6, 11.5	< 0.005
Week 12	32.2	25.4	17.5	3.5, 10.1	< 0.005
Week 22	23.1	18.6	13.2	1.5, 7.5	< 0.005
Week 26	20.3	16.9	12.2	0.5, 6.2	0.021
Week 52	15.7	12.7	9.9	0.4, 5.5	0.024

Safety

With respect to safety in the CEASE study, there was no dose response relationship with AEs except for nausea and vomiting (7.3% in the 25 mg group vs. 5.4% in the 15 mg group).

In this study, there were four deaths:

- two myocardial infarctions: one in a 58 years old man who had stopped study medication 3.5 month prior to the event and one in a 59 years old man who was probably on treatment with a 25 mg patch
- one boat accident
- one cardiac arrhythmia secondary to thyrotoxicosis

There were two additional non-fatal cases of myocardial infarctions, one occurring in a 66 years old mail who was randomised to placebo and one in a 50 years old man who was randomised to the 15 mg patch but was off treatment for a few weeks when the event occurred.

Additional serious adverse events included five surgical operations, planned or acute, and two accidents.

Conclusion

In summary, this clinical study demonstrates the advantage of a higher dose of nicotine patches (25 mg compared to 15 mg) in successful smoking cessation among heavy smokers. Specifically, the rate of continuous smoking cessation at one-year follow-up was 3% higher in those subjects who received a 25 mg patch compared to those who received a 15 mg patch. Although this difference is not large, it can still represent an important advantage in terms of public health gains, due to the relatively high proportion of smokers in the general population and the high morbidity associated with smoking.

In a tolerability study of the new NNTP formulation of Nicorette patches safety is sufficiently demonstrated.

Risk management plan

The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks. The safety profile of NNTP is expected to be similar to that of Nicorette. Local tolerability/administration disorders will be closely monitored for Nicorette Invisi patch and this will be addressed in the PSURs.

Product information

SPC

The content of the SPC approved during the national procedure is in accordance with that accepted for Nicorette transdermal patches. The non-clinical findings on local tolerance are adequately reflected in the SPC.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 5 participants, followed by two rounds: one with 20 participants and a second round with 30 participants. The results of the pilot round were satisfactory; no major changes were made to the PL. The final version of the leaflet was approved by the readers, since all question reached the 90%/90% threshold. The total score for the second group was significantly higher than the score for the first group, meaning that the changes made to the leaflet after phase one had a positive effect. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Nicorette Invisi pleister 10 mg, transdermal patch 10 mg/16 hours, Nicorette Invisi pleister 15 mg, transdermal patch 15 mg/16 hours and Nicorette Invisi pleister 25 mg, transdermal patch 25 mg/16 hours have a proven chemical-pharmaceutical quality and are approvable line extensions to Nicorette 5 mg, Nicorette 10 mg and Nicorette 15 mg transdermal patches. Nicorette is a well-known medicinal product with an established favourable efficacy and safety profile.

For this application the MAH refers to the Nicorette transdermal patch dossier. In addition three pharmacokinetic studies were conducted to investigate the relationship between the released nicotine dose to the new nicotine transdermal patch (NNTP) area in comparison to Nicorette patches, to evaluate dose proportionality and to demonstrate bioequivalence between the NNTP and the marketed Nicorette patch. The results from these studies indicate that the desired release rate was obtained with the smaller patch sizes, and that the AUC and C_{max} increased linear with the dose (and patch size). In addition, the MAH has carried out a study to examine the use of higher doses (25 mg Nicorette® patches) in heavy smokers (> 15 cigarettes a day). Bioequivalence was demonstrated for NNTP 22.5 cm² (release rate 25 mg/16h) with marketed Nicorette 50 cm² patches (20 + 30 cm²; total release rate 25 mg/16h). Overall, the study results did not raise any new safety concerns regarding treatment with Nicorette Invisi patches.

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

In the Board meeting of 16 July 2009, the application was discussed. Concerns regarding local toxicity of the new patch were addressed, as well as potential harm when patches are worn for 24 hours. The MAH sufficiently demonstrated that local tolerability scores were mild. No excessive harm is expected when the patches are worn for 24 hours or more; the MAH demonstrated that this did not lead to significant safety problems.

The MEB, on the basis of the data submitted, considered that that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Nicorette Invisi pleister 10 mg, transdermal patch 10 mg/16 hours, Nicorette Invisi pleister 15 mg, transdermal patch 15 mg/16 hours and Nicorette Invisi pleister 25 mg, transdermal patch 25 mg/16 hours were authorised in the Netherlands on 25 October 2010.

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
NNTP	New Nicotine Transdermal Patch
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
TTS	Transdermal Therapeutic system
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
Transfer of the marketing authorisation.	--	MA transfer	16-5-2008	21-11-2009	Approval	N